Horizon scanning report

March 2009

Hypomethylating agents in the treatment of myelodysplastic syndromes

Pamela Smartt

Health Services Assessment Collaboration (HSAC), University of Canterbury

ISBN 978-0-9864563-6 (online)
ISBN 978-0-9864563-4-3 (print)

ISSN 1178-5748 (online)
ISSN 1178-573X (print)
Review Team
This review was undertaken by the Health Services Assessment Collaboration (HSAC). HSAC is a collaboration of the Health Sciences Centre of the University of Canterbury, New Zealand and Health Technology Analysts, Sydney, Australia. This report was authored by Dr Pamela Smartt, Senior Research Fellow, who developed and undertook the literature search, extracted the data, conducted the critical appraisals, and prepared the report.

Acknowledgements
David Brinson, Researcher, peer reviewed the final draft. Cecilia Tolan, Administrator, provided document formatting. Franziska Gallrach and Carmel Olsen, Research Assistants, assisted with retrieval of documents.

Staff at the University of Canterbury Libraries assisted with the retrieval of articles.

The current review was conducted under the auspices of a contract funded by the New Zealand Ministry of Health. This report was requested by Ricarda Vandervorst, Senior Analyst, Sector Capability and Innovation Directorate, of the New Zealand Ministry of Health. We thank Peter Browett, Clinical Haematologist and Professor of Pathology, Department of Molecular Medicine and Pathology, University of Auckland for his careful peer review of this report and helpful comments. We also thank Kate Garland, Senior Analyst, Sector Capability and Innovation Directorate, of the New Zealand Ministry of Health, for her help to finalise the report.

Copyright Statement and Disclaimer
This report is copyright. Apart from any use as permitted under the Copyright Act 1994, no part may be reproduced by any process without written permission from HSAC. Requests and inquiries concerning reproduction and rights should be directed to the Director, Health Services Assessment Collaboration, Health Sciences Centre, University of Canterbury, Private Bag 4800, Christchurch, New Zealand

HSAC takes great care to ensure the accuracy of the information in this report, but neither HSAC, the University of Canterbury, Health Technology Analysts Pty Ltd nor the Ministry of Health make any representations or warranties in respect of the accuracy or quality of the information, or accept responsibility for the accuracy, correctness, completeness or use of this report.

The reader should always consult the original database from which each abstract is derived along with the original articles before making decisions based on a document or abstract. All responsibility for action based on any information in this report rests with the reader.

This report is not intended to be used as personal health advice. People seeking individual medical advice should contact their physician or health professional.

The views expressed in this report are those of HSAC and do not necessarily represent those of the University of Canterbury New Zealand, Health Technology Analysts Pty Ltd, Australia or the Ministry of Health.
Contact Details

Health Services Assessment Collaboration (HSAC)
Health Sciences Centre
University of Canterbury
Private Bag 4800
Christchurch 8140
New Zealand
Tel: +64 3 345 8147  Fax: +64 3 345 8191

Email: hsac@canterbury.ac.nz
Web Site: www.healthsac.net
Executive Summary

Myelodysplastic syndrome(s)

Myelodysplastic syndrome(s) (MDS) comprise a heterogeneous group of rare life-threatening diseases characterised by ineffective haematopoiesis leading to peripheral blood cytopenias (low red white or platelet counts) and progressive bone marrow failure. The initiating event is thought to be mutation in the bone marrow/blood stem cells. For poor prognosis patients the median survival is five months. Disease related death is usually from bleeding, infection or progression to acute myelogenous leukaemia (AML).

MDS can arise de novo (primary MDS) or following treatment with chemotherapy, radiation therapy or chemical injury (secondary MDS). Between 35 to 40% of cases transform to acute myelogenous leukaemia (AML) which is often refractory to standard treatment, with most patients dying from infection or bleeding.

The clinical presentation of MDS is generally non-specific. The diagnosis and classification of MDS is based on two classification systems, the French-American-British classification system and the more recent updated World Health Organisation system. The International Prognostic Scoring System (IPSS) provides a method for evaluating clinical prognostic risk factors for patients with MDS based on scores for cytogenetic sub-group, percentage of blasts in the bone marrow and the number of cytopenias.

Burden of disease

In 2004 there were 391 new registrations of MDS in New Zealand and an estimated crude incidence rate of approximately 9.5 per 100,000 persons. Most patients were registered as having an unspecified myelodysplastic syndrome (according to the ICD-10-AM diagnosis code D46.9). A slightly higher proportion of males than females were registered. Most new registrations in 2005 were in persons over the age of 70 years.

Treatment options

MDS patients are a challenging treatment group and a range of treatments are in use worldwide. For low risk patients, where the goal of treatment is haematological improvement and an age-appropriate quality of life, low intensity treatment with cytotoxic and non-cytotoxic drugs and adjuvant supportive care may be used. Hypomethylating agents may be administered to suitable patients. For higher risk patients, treatment is directed at altering the natural history of the disease to improve survival and delay progression to AML. Treatment options include aggressive cytotoxic therapy, hematopoietic stem cell transplantation and supportive care. Low dose hypomethylating agents may be administered to high-risk older patients, with low performance status and co-morbid disease who are not eligible for high dose/intensive therapeutic options.

In New Zealand, there are very limited treatment options for patients with MDS. All patients receive supportive care – i.e. transfusion support and treatment of infective episodes. Older patients\(^1\) with low blast count AML (previously RAEB-T) who are not candidates for intensive AML induction chemotherapy, may be offered low dose Cytarabine (ara-C). A

---

\(^1\) Median age of MDS 70 – 75;
small number of patients’ may be considered for allogeneic hematopoietic stem cell transplantation (HSCT).

The comparator
Supportive care is the comparator of choice. All patients diagnosed with MDS receive supportive care to control/treat side effects (anaemia, neutropenia, and thrombocytopenia), improve quality of life and prevent/treat complications. The nature and extent of supportive care varies from centre to centre and depends on a number of factors including (a) the severity of the cytopenias, (b) new developments in care standards and (c) new developments in pharmaceuticals and their availability.

Hypomethylating agents (azacitidine and decitabine)
Aberrant methylation of DNA cytosine residues can silence genes that are essential for the control of normal cell growth and differentiation. MDS is characterised by the hypermethylation/silencing of multiple genes. Hypomethylating agents can reverse this process by inhibiting DNA methyltransferase (DNMT).

Azanucleoside DNMT inhibitors, 5-aza-2’-deoxycytidine (decitabine) and 5-azacitidine (azacitidine), have been shown to have clinical activity in MDS and acute leukaemia patients. Azacitidine and decitabine have at least two mechanisms of action; cytotoxicity at higher doses resulting from incorporation into RNA or DNA, and DNA demethylation at lower doses due to DNMT inhibition.

Inhibition of DNA methylation is responsible for the clinical efficacy of these azanucleosides. Both drugs have been approved for the treatment of MDS in the USA and Europe. Three previous brief horizon scan reports have been published. No published systematic reviews were identified.

Safety
The hypomethylating agents (azacitidine and decitabine), when administered at clinically effective doses, are well tolerated with manageable side effects. The main adverse event associated with the use of these agents is myelosuppression including neutropenia, thrombocytopenia and anaemia.

Grade 3–4 haematological toxicity occurred in <5% of patients in phase III trials. Non haematological toxicities included nausea, vomiting, diarrhoea, constipation, and injection site reactions.

Safety evaluation of these agents is confounded by the pathophysiology of MDS, which overlaps with the most common toxicities of azanucleosides.

Effectiveness
Myelodysplastic syndrome severely affects the patient’s quality of life and, until recently, available treatments for older patients have been very limited.

---

2 Upper age limit for allogeneic HSCT is 60 – 65, plus donor availability – therefore is only an option for 5% of patients.
The hypomethylating agents (azacitidine and decitabine) have shown survival benefit in clinical trials in these patients. Promising (though relatively low) response rates in early phase II trials in both agents led to the initiation of randomised controlled trials designed to confirm the phase II studies response rates and establish if treatment with these agents conferred a survival advantage and/or delayed progression to AML. The key features of these trials were the achievement of:

- durable response rates
- delayed time to progression to AML
- a manageable toxicity profile.

While approval for the use of azacitidine and decitabine has been obtained from the FDA for all FAB sub-types of MDS, the best responses have been demonstrated in patients with:

- poor prognosis disease e.g. patients with chromosome 7 irregularities
- older age
- AML by newer classifications (20-30% blasts).

Treatment with the hypomethylating agents (azacitidine and decitabine) has also resulted in a substantially improved quality of life for patients coupled with reduced reliance on transfusions and delayed time to transformation to AML. Particular improvements have been reported in overall health status, fatigue, dyspnea and psychological state.

**Levels of evidence**

There were no systematic reviews (Evidence Level I, Appendix I) of the effectiveness of azacitidine or decitabine in the treatment of MDS. There were three randomised controlled trials (two providing Level II Evidence and one Level III-1Evidence) of the effectiveness of azacitidine therapy in MDS (Appendix B, Tables 9-16). There were three randomised controlled trials (all Evidence Level II) of the effectiveness of decitabine therapy in MDS (Appendix C, Tables 17-24). The remaining studies examined in this report were case series (Evidence Level IV). The quality of the randomised controlled trials was not assessed.

**Conclusion**

Data from randomised controlled trials of the hypomethylating agents (azacitidine and decitabine) indicate that, for the first time, the natural history of MDS may be changed by non-intensive therapy with an acceptable toxicity profile. Recent trials have shown a survival benefit in patients treated with these agents when compared to patients treated with supportive or conventional care. High risk older patients, with low performance status and co-morbid disease who are not eligible for high dose/intensive therapeutic options currently form the bulk of the patient population treated with hypomethylating agents. There have also been randomised controlled trials to establish the most effective dose schedule. However, morphologic evidence of disease rarely disappears with treatment and several courses may be needed for best response. Clinical trials of combination therapy incorporating hypomethylating agents are ongoing.
Table of Contents

Review Team ............................................................................................................. i
Acknowledgements ................................................................................................... i
Copyright Statement and Disclaimer ....................................................................... i
Contact Details ......................................................................................................... ii
Executive Summary .................................................................................................. iii
  Myelodysplastic syndrome(s) .................................................................................. iii
  Burden of disease .................................................................................................... iii
  Treatment options ................................................................................................... iii
  The comparator ........................................................................................................ iv
  Hypomethylating agents (azacitidine and decitabine) .............................................. iv
  Safety ....................................................................................................................... iv
  Effectiveness ........................................................................................................... iv
  Levels of evidence ................................................................................................... v
  Conclusion ................................................................................................................ v
Table of Contents .................................................................................................... vi
List of Tables ............................................................................................................ ix
List of Figures ........................................................................................................... xi
List of Abbreviations and Acronyms ......................................................................... xii
Background ............................................................................................................ 1
Myelodysplastic Syndrome(s) (MDS) ....................................................................... 3
  Disease natural history ....................................................................................... 4
  Disease classification and prognosis ............................................................... 5
  The World Health Organisation Classification (WHO) ...................................... 6
  Other prognostic systems ................................................................................... 6
  Summary ............................................................................................................... 6
Clinical Need and Burden of Disease ....................................................................... 7
  Summary ............................................................................................................... 8
Treatment and Management of MDS ..................................................................... 9
  Treatment goals .................................................................................................... 9
  Lower risk MDS .................................................................................................. 9
  Higher risk MDS ................................................................................................ 10
  Treatment algorithm ......................................................................................... 10
  Summary ............................................................................................................. 12
  Assessment of treatment outcomes ............................................................... 12
The Comparator .................................................................................................................. 15
The Technology .................................................................................................................. 17
   Hypomethylating agents ................................................................................................. 17
   Stage of development of the technology ........................................................................ 17
   Summary ......................................................................................................................... 18
Methods .................................................................................................................................. 19
   Previous Horizon Scan reports ...................................................................................... 21
   Levels of evidence .......................................................................................................... 21
Clinical Outcomes: Safety .................................................................................................. 23
   Azacitidine: FDA safety assessment of azacitidine ......................................................... 23
   Decitabine: FDA safety assessment of decitabine .......................................................... 26
   Summary ......................................................................................................................... 27
Clinical Outcomes: Effectiveness ....................................................................................... 29
   Azacitidine ...................................................................................................................... 29
   The Cancer and Leukemia Group B (CALGB) trials ..................................................... 29
   Community dosing schedules ....................................................................................... 33
   New developments and ongoing clinical trials ............................................................... 35
   Decitabine ...................................................................................................................... 35
      Clinical studies forming the basis for FDA approval ................................................... 35
      Post FDA approval studies ....................................................................................... 38
   New developments and ongoing clinical trials ............................................................... 39
Clinical Outcomes: Quality of Life .................................................................................... 41
   Azacitidine ...................................................................................................................... 41
   Decitabine ...................................................................................................................... 41
   Summary ......................................................................................................................... 42
Potential Cost Impact ........................................................................................................ 43
Ethical Considerations ....................................................................................................... 45
Training and Accreditation ............................................................................................... 47
   Treatment guidelines ..................................................................................................... 47
Limitations of the Assessment .......................................................................................... 49
References .......................................................................................................................... 51
Appendix A: International Working Group (IWG) Response Criteria ......................... 57
   Altering disease natural history ..................................................................................... 57
      Complete remission (CR) ............................................................................................ 57
      Partial remission (PR) ................................................................................................. 57
      Stable disease ............................................................................................................ 57
      Failure ....................................................................................................................... 57
      Relapse after CR or PR (one or more of the following) .............................................. 57
Hypomethylating agents in the treatment of myelodysplastic syndromes
<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>57</td>
</tr>
<tr>
<td>Disease transformation</td>
<td>58</td>
</tr>
<tr>
<td>Survival and progression-free survival</td>
<td>58</td>
</tr>
<tr>
<td>Cytogenetic response</td>
<td>58</td>
</tr>
<tr>
<td>Quality of life</td>
<td>58</td>
</tr>
<tr>
<td>Hematologic improvement (HI)</td>
<td>58</td>
</tr>
<tr>
<td>Erythroid response (HI-E)</td>
<td>58</td>
</tr>
<tr>
<td>Platelet response (HI-P)</td>
<td>59</td>
</tr>
<tr>
<td>Neutrophil Response (HI-N)</td>
<td>59</td>
</tr>
<tr>
<td>Progression/relapse after HI</td>
<td>59</td>
</tr>
<tr>
<td>Appendix B: Azacitidine Evidence Tables</td>
<td>61</td>
</tr>
<tr>
<td>Appendix C: Decitabine Evidence Tables</td>
<td>73</td>
</tr>
<tr>
<td>Appendix D: Hazard Ratios for Sub-populations</td>
<td>81</td>
</tr>
<tr>
<td>Appendix E: Recruiting Azacitidine Trials (clinical trials.govt)</td>
<td>83</td>
</tr>
<tr>
<td>Appendix F: New and Recruiting Decitabine Trials (clinical trials.govt)</td>
<td>89</td>
</tr>
<tr>
<td>Appendix G: Overview of azacitidine studies</td>
<td>93</td>
</tr>
<tr>
<td>Appendix H: CALGB Studies</td>
<td>95</td>
</tr>
<tr>
<td>Appendix I: Levels of Evidence</td>
<td>97</td>
</tr>
<tr>
<td>Explanatory notes</td>
<td>98</td>
</tr>
<tr>
<td>Table</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>Table 1:</td>
<td>Overall survival and time to 25% AML progression for untreated MDS patients according to IPSS risk categories</td>
</tr>
<tr>
<td>Table 2:</td>
<td>The French-American-British (FAB) classification of Myelodysplastic Syndromes</td>
</tr>
<tr>
<td>Table 3:</td>
<td>New registrations of myelodysplastic syndromes in New Zealand 2004-2005</td>
</tr>
<tr>
<td>Table 4:</td>
<td>Population characteristics of newly registered myelodysplastic syndromes in New Zealand 2004-2005</td>
</tr>
<tr>
<td>Table 5:</td>
<td>Operational definitions used to report key outcomes in pivotal RCTs of hypomethylating agents</td>
</tr>
<tr>
<td>Table 6:</td>
<td>Search strategy for hypothemylating agents for MDS</td>
</tr>
<tr>
<td>Table 7:</td>
<td>Grade 3 or 4 haematological toxicity by treatment group</td>
</tr>
<tr>
<td>Table 8:</td>
<td>Selected grade 3/4 adverse events in patients treated with different dosing regimens of azacitidine who received ≥ 1 dose of azacitidine as of March 31, 2007</td>
</tr>
<tr>
<td>Table 9:</td>
<td>Silverman et al (1993)</td>
</tr>
<tr>
<td>Table 10:</td>
<td>Silverman et al. (1994)</td>
</tr>
<tr>
<td>Table 11:</td>
<td>Silverman et al. (2002)</td>
</tr>
<tr>
<td>Table 12:</td>
<td>Kornblith et al. (2002)</td>
</tr>
<tr>
<td>Table 13:</td>
<td>Raza et al. (2008)</td>
</tr>
<tr>
<td>Table 14:</td>
<td>Fenaux et al. (2009)</td>
</tr>
<tr>
<td>Table 15:</td>
<td>Lyons et al (2007)</td>
</tr>
<tr>
<td>Table 16:</td>
<td>Muller-Thomas et al (2009)</td>
</tr>
<tr>
<td>Table 17:</td>
<td>Wijermans et al (1997)</td>
</tr>
<tr>
<td>Table 18:</td>
<td>Wijermans et al (2000)</td>
</tr>
<tr>
<td>Table 19:</td>
<td>Wijermans et al (2005)</td>
</tr>
<tr>
<td>Table 20:</td>
<td>Kantarjlan et al. (2006)</td>
</tr>
<tr>
<td>Table 21:</td>
<td>Kantarjian et al. (2007)</td>
</tr>
<tr>
<td>Table 22:</td>
<td>Ruter et al (2007)</td>
</tr>
<tr>
<td>Table 23:</td>
<td>Wijermans, Ruter et al (2008)</td>
</tr>
<tr>
<td>Table 24:</td>
<td>Wijermans, Suciu et al. (2008)</td>
</tr>
<tr>
<td>Table 25:</td>
<td>Overview of azacitidine studies to support efficacy in MDS patients</td>
</tr>
<tr>
<td>Table 26:</td>
<td>CALGB studies - Summary of response assessment (ITT)</td>
</tr>
</tbody>
</table>
Table 27: NHMRC Evidence hierarchy: designations of “levels of evidence” according to type of research question (including explanatory notes). ................................................................. 97
### List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Haematopoiesis: the normal development of blood cells.</td>
<td>3</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Age distribution of newly registered cases of myelodysplastic syndromes in New Zealand 2004.</td>
<td>8</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Treatment algorithm for MDS based on the NCCN guidelines.</td>
<td>11</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Flow diagram for patients entered into a Phase III trial.</td>
<td>32</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Kaplan-Meier survival curves for patients with MDS treated with azacitidine or conventional care.</td>
<td>33</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Study design used by Lyons and Cosgriff (2009) to evaluate three different schedules for azacitidine in a community setting.</td>
<td>34</td>
</tr>
<tr>
<td>Figure 7A</td>
<td>Time to AML or death for all patients treated with decitabine versus supportive care.</td>
<td>37</td>
</tr>
<tr>
<td>Figure 7B</td>
<td>Time to AML or death for treatment naive patients treated with decitabine or supportive care.</td>
<td>38</td>
</tr>
<tr>
<td>Figure 7C</td>
<td>Time to AML or death for IPSS INT-2 and high-risk patients treated with decitabine or supportive care.</td>
<td>38</td>
</tr>
<tr>
<td>Figure 8</td>
<td>Hazard ratios and 95% confidence intervals for overall survival in the intention to treat analysis.</td>
<td>81</td>
</tr>
</tbody>
</table>
### List of Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>Acute myelogenous leukaemia</td>
</tr>
<tr>
<td>ARA-C</td>
<td>Cytarabine</td>
</tr>
<tr>
<td>ATRA</td>
<td>All-trans retinoic acid</td>
</tr>
<tr>
<td>AZA</td>
<td>Azacitidine</td>
</tr>
<tr>
<td>BM</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>CALGB</td>
<td>Cancer and Leukemia Group B</td>
</tr>
<tr>
<td>CMML</td>
<td>Chronic myelomonocytic leukemia</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>DAC</td>
<td>Dacogen, Decitabine</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DNMT</td>
<td>DNA methyltransferase</td>
</tr>
<tr>
<td>EORTC</td>
<td>European organisation for research into treatment for cancer</td>
</tr>
<tr>
<td>FAB</td>
<td>French-American-British classification</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>HSCT</td>
<td>Haematopoietic stem cell transplant</td>
</tr>
<tr>
<td>ICD=10</td>
<td>10th Edition International Classification of Disease</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenous</td>
</tr>
<tr>
<td>IPSS</td>
<td>International Prognostic Scoring System</td>
</tr>
<tr>
<td>IWG</td>
<td>International working group</td>
</tr>
<tr>
<td>MDS</td>
<td>Myelodysplastic syndrome(s)</td>
</tr>
<tr>
<td>NCCH</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression free survival</td>
</tr>
<tr>
<td>p15INK4b</td>
<td>Cell cycle inhibitory protein</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RAEB</td>
<td>Refractory anaemia with excess blasts</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>Refractory anaemia with excess blasts in transformation</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>s.c</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SC</td>
<td>Supportive care</td>
</tr>
<tr>
<td>tAML</td>
<td>Therapy related AML</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VPA</td>
<td>Valproic acid</td>
</tr>
</tbody>
</table>
Background

The myelodysplastic syndrome(s) (MDS) comprise a group of heterogeneous haematological disorders characterised by a greatly reduced production of one or more blood cell types. For poor prognosis patients the median survival is 5 months. Disease related death is usually from bleeding, infection or progression to acute myelogenous leukaemia (AML) (Gryn, et al., 2002). For most patients with MDS, advancing age and co-morbidities reduce the ability to withstand intensive therapy and treatment options to date have been limited. Supportive care is administered to all patients and is the standard of care for most.

Recent efforts to improve quality of life and prolong survival in MDS patients have produced new therapeutic options which have undergone intensive testing in clinical trials. Of particular clinical significance has been the clinical development of hypomethylating agents. This report examines the following questions relating to the use of these agents in MDS:

Q1. What is the clinical benefit of hypomethylating agents for myelodysplastic syndromes in improving outcomes in terms of:

- overall survival (OS)
- time to progression (PFS)
- quality of life (QOL)?

Q2. What are the side effects of this treatment?
Hypomethylating agents in the treatment of myelodysplastic syndromes
Myelodysplastic Syndrome(s) (MDS)

Myelodysplastic syndrome(s) (MDS) comprise a heterogeneous group of rare life-threatening disorders of haematopoiesis. They are characterised by peripheral cytopenia, and dysplastic changes of the cell lineages of erythropoiesis, granulopoiesis and megakaryopoiesis in the bone marrow which lead to progressive bone marrow failure. The initiating event is thought to be a mutation in the bone marrow/blood stem cells. For poor prognosis patients the median survival is 5 months. Disease related death is usually from bleeding, infection or progression to acute myelogenous leukaemia (AML). Between 35 to 40% of cases transform to acute myelogenous leukaemia (AML) and most patients die from infection or bleeding.

In MDS patients the bone marrow is more active than normal. However, the number of blood cells in the circulatory system is reduced because most of the cells produced by the hyperactive marrow are defective and destroyed before they leave the marrow. Thus the hallmark of MDS is the combination of a hyperactive marrow with low blood cell counts. Clinically, this ineffective haematopoiesis (Figure 1) manifests as anaemia (low red blood cell count), neutropenia (low white cell count), and thrombocytopenia (reduced platelet count). Abnormality in the appearance of the bone marrow and blood cells is a common feature of MDS. These abnormalities (e.g. white cells lacking normal granules) are characteristic of the condition.

![Figure 1: Haematopoiesis: the normal development of blood cells. The progenitor cells (blood stem cell) are found in the marrow where they undergo differentiation to form mature blood cells of various types (red and white blood cells and platelets). When mature these cells migrate from the bone marrow to the peripheral blood.](image)

[3] The process by which new blood cells are formed, usually taking place in the bone marrow
MDS differs from leukaemia in that the production of any type of blood cell may be affected.

**Disease natural history**

MDS occurs mainly in the elderly. It has a variable natural history and requires risk adapted management strategies. Approximately half of MDS patients are asymptomatic at presentation and are diagnosed only after routine laboratory tests showing peripheral blood abnormalities. The most common presenting characteristic is low red blood cell count (anaemia). MDS may arise de novo, or after treatment with chemotherapy or radiation for other diseases. Secondary myelodysplasia usually has a poorer prognosis. Approximately one third of all cases of MDS transform to acute myeloid leukaemia (AML) at a rate that varies between a few months to many years. Transformed AML is much less responsive to chemotherapy than de novo AML.

The median survival for MDS patients varies from 0.4 years in higher risk patients to 5.7 years in lower risk patients (Greenberg, et al., 1997; Muller-Berndorff, Haas, Kunzmann, Schulte-Monting, & Lubbert, 2006). Patients undergoing acute leukaemic transformation have a survival period of 6-12 months (Saba, 2008). Significant predictors of both survival and AML evolution include bone marrow (BM) blast percentage, number of peripheral blood cytopenias, and cytogenetic subgroup (karyotype). These predictors are used to determine the patients risk category according to expected survival and progression to AML.

The median survival and the time to 25% AML progression for untreated MDS patients in different risk categories is shown in **Table 1**.

**Table 1:** Overall survival and time to 25% AML progression for untreated MDS patients according to IPSS risk categories (National Comprehensive Cancer Network (2009))

<table>
<thead>
<tr>
<th>International Prognostic Scoring System Risk Category</th>
<th>% BM blasts</th>
<th>Karyotype</th>
<th>Cytopenias</th>
<th>Median survival (yrs)</th>
<th>25% AML progression (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;5</td>
<td>good†</td>
<td>0 or 1</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>5-10</td>
<td>Intermediate/poor‡</td>
<td>2 or 3</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>11-30</td>
<td>NA</td>
<td>NA</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>High</td>
<td>&gt;30</td>
<td>NA</td>
<td>NA</td>
<td>0.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

† del(5q) or del(20q), ‡ other abnormalities not including del(5q) or del(20q). BM=bone marrow.

4In chronic lymphocytic leukaemia (CLL) and chronic myeloid leukaemia (CML) there is an increased production of lymphoid or myeloid cells. In acute myeloid leukaemia (AML) there is an increase in myeloid blasts, which replace the normal bone marrow, resulting in impaired production of the normal blood cells – i.e. all 3 lineages.
Disease progression in MDS patients is characterised by:

- an increased percentage of BM blasts/transformation to AML
- progressive pancytopenia (reduction in the number of red and white blood cells and platelets)
- increasing transfusion needs (dependency on red cell and platelet transfusions) (Garcia-Manero, Shan, et al., 2008)
- increased number of infections.

Disease classification and prognosis

A variety of MDS classification systems have been developed over the last 20 years to predict (a) the overall survival of patients with MDS and (b) the evolution from MDS to AML. All of these systems are based to a greater or lesser extent on features of the disease which have been associated with *risk and prognosis*. The most well known classification systems for MDS are the:

- French-American-British classification (FAB) (Bennett, et al., 1982)
- World Health Organisation classification (WHO) (Harris, et al., 1999).

The original French-American-British (FAB) classification (Bennett, et al., 1982) comprised of five disease entities distinguished on blast count, lineage commitment, and level of differentiation of the neoplastic cells using morphologic, cytochemical, and immunophenotypic features (Leukaemia Research, 2009). Clinicians and researchers have considerable experience with the FAB classification and it is still very popular (*Table 2*). It has been used in most of the key studies reported in this horizon scan.

### Table 2: The French-American-British (FAB) classification of Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>FAB group</th>
<th>Acronym</th>
<th>% Of all cases</th>
<th>% trans AML</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anaemia</td>
<td>RA</td>
<td>30-45</td>
<td>10</td>
<td>Blast cell % not significantly increased, red and white cell count may be low.</td>
</tr>
<tr>
<td>Refractory anaemia with ringed sideroblasts</td>
<td>RARS</td>
<td>15</td>
<td>8</td>
<td>As above but with additional RBC abnormalities. RBC precursors are unable to use iron normally and it deposited as characteristic rings in these cells.</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts</td>
<td>RAEB</td>
<td>15</td>
<td>40</td>
<td>Increased (5-20%) blast cells in the marrow. There may be reduced counts of all blood cells.</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts in transformation</td>
<td>RAEB-T</td>
<td>5-15</td>
<td>60-75</td>
<td>Higher promotion of blast cells in marrow (20-30%). Treatment is similar to AML</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
<td>CMML</td>
<td>15</td>
<td>15-30</td>
<td>White cells (monocytes) increased to &gt;1x10⁹/litre. The marrow may or may not contain an increased % of blast cells. Has features of myeloproliferative disorders.</td>
</tr>
</tbody>
</table>

5 Difference between RAEB, RAEB-T and AML are based on bone marrow blast cell percentages – in leukaemia there are over 30% blasts in the marrow.
The World Health Organisation Classification (WHO)

The World Health Organisation Classification of Myeloid Neoplasms (Harris, et al., 1999) takes into account genetic (e.g. 5q-syndrome) and clinical (e.g. prior therapy) features. The WHO classification differs from the FAB classification in several important areas:

- chronic myelomonocytic leukemia (CMML) is not included with MDS
- disorders with greater than 20% BM blasts are classified as AML
- MDS with multi-lineage dysplasia is considered be a separate entity.

The WHO classification (and its associated prognostic scoring system) has been less widely adopted in the USA as it is not routinely performed in community hospitals there (Garcia-Manero, 2008). In New Zealand, most laboratories now use the WHO classification.

Other prognostic systems

- A WHO classification-based prognostic scoring system (WPSS) was reported by (Bernasconi, et al., 2007)
- The MD Anderson Cancer Center (Verstovsek, et al., 2008) has generated a new prognostic scoring system which takes into account factors associated with poor survival and also divides IPSS lower risk MDS patients into 3 further categories.

Summary

Myelodysplastic syndrome is a rare life-threatening disease characterised by ineffective haematopoiesis leading to peripheral blood cytopenias and progressive bone marrow failure. The initiating event is thought to be a mutation in the bone marrow/blood stem cells. MDS can arise de novo (primary MDS) or following treatment with chemotherapy, radiation therapy or chemical injury (secondary MDS). Between 35-40% of cases transform to acute myelogenous leukaemia (AML) which is often refractory to standard treatment with most patients dying from infection or bleeding. The clinical presentation of MDS is generally non-specific. The diagnosis and classification of MDS is based on two classification systems, the French-American-British classification system and the more recent updated WHO system. The International Prognostic Scoring System provides a method for evaluating clinical prognostic risk factors for patients with MDS based on scores for cytogenetic sub-group, percentage of blasts in the bone marrow and number of cytopenias (low red cell, white cell or platelet counts).
Clinical Need and Burden of Disease

For the purpose of reporting the New Zealand burden of this disease, MDS is defined as all cases assigned the ICD-10-AM code D46. This definition includes refractory anaemia, refractory anaemia with ring sideroblasts, refractory anaemia with excess blasts and refractory anaemia with excess blasts in transformation and excludes chronic myelomonocytic leukaemia. It should also be noted that in New Zealand many elderly cases are not subjected to a diagnostic bone marrow procedure and are therefore not registered in the national statistics, while in the USA there is no central registry (National Horizon Scanning Centre, 2007). MDS statistics for these countries (as for others) are likely to be an underestimate of the true incidence and burden of MDS.

In 2004 there were 391 new registrations for MDS. Most patients were registered as having an unspecified myelodysplastic syndrome (Table 3).

Table 3: New registrations of myelodysplastic syndromes in New Zealand 2004-2005

<table>
<thead>
<tr>
<th>ICD-10 code †</th>
<th>Name of disorder</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>D461</td>
<td>Refractory anaemia with sideroblasts</td>
<td>39</td>
</tr>
<tr>
<td>D462</td>
<td>Refractory anaemia with excess of blasts</td>
<td>22</td>
</tr>
<tr>
<td>D463</td>
<td>Refractory anaemia with excess of blasts with transformation</td>
<td>3</td>
</tr>
<tr>
<td>D464</td>
<td>Refractory anaemia, unspecified</td>
<td>82</td>
</tr>
<tr>
<td>D467</td>
<td>Other myelodysplastic syndromes</td>
<td>25</td>
</tr>
<tr>
<td>D469</td>
<td>Myelodysplastic syndrome, unspecified</td>
<td>220</td>
</tr>
</tbody>
</table>

Myelodysplastic disorder total 391

† http://www.who.int/classifications/icd/en/

A higher proportion of males than females were registered in 2004 (Table 4). Maori were under represented.

Table 4: Population characteristics of newly registered myelodysplastic syndromes in New Zealand 2004-2005

<table>
<thead>
<tr>
<th>Attribute</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>155 (39.6%)</td>
</tr>
<tr>
<td>Males</td>
<td>236 (60.4%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>9 (2.3%)</td>
</tr>
<tr>
<td>Pacific people</td>
<td>8 (2.0%)</td>
</tr>
<tr>
<td>Asian/Indian</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>European/Other</td>
<td>368 (94.1%)</td>
</tr>
</tbody>
</table>

Total MDS (ICD-10-AM D46) population 391
The incidence of MDS (ICD-10-AM code D46) increases with age. Figure 2 illustrates a steep increase in registrations after the age of 65 years with over 80% of new registrations occurring in persons over the age of 70 years.

Figure 2: Age distribution of newly registered cases of myelodysplastic syndromes in New Zealand 2004

The crude population rate of MDS (ICD-10-AM diagnosis code D46) in 2004 in New Zealand is estimated as 9.6 per 100,000. This compares with a reported prevalence of approximately 11 to 30 per 100,000 persons in the EU population and an estimated 5 per 100,000 in the USA (Siddiqui & Scott, 2005). The incidence increases with age — incidence in the over 70s is reported to be >30 per 100,000.

Summary

In 2004 there were 391 new registrations of MDS (all cases assigned ICD-10-AM diagnosis code D46) in New Zealand and an estimated minimum incidence of approximately 9.6 per 100,000 persons. Most patients were registered (according to the ICD-10-AM classification) as having unspecified myelodysplastic syndrome (D46.9). A slightly higher proportion of males than females were registered. Most new registrations in 2004 were in persons over the age of 70 years.

Direct comparisons however may be misleading as there are variations in the disease entities included
Treatment and Management of MDS

Treatment goals

MDS patients are a challenging treatment group, due (a) to their advanced age, (b) co-morbidities, (c) inability to tolerate intensive therapy and (d) the unusual combination of hyperactive marrow but inadequate blood cell production. Management and treatment goals for MDS patients vary according to prognosis and IPSS risk group (Cheson, et al., 2000). For lower risk MDS\(^7\) where apoptosis (cell death) is the main feature, the goal of treatment is haematological improvement\(^8\) and an age-appropriate quality of life. For higher risk\(^9\) patients treatment is directed at altering the natural history of the disease to improve survival and delay progression to AML (NCCN, 2009). As the understanding and classification of MDS has improved, the number of treatment options has increased. Currently these include:

- best supportive care for patients with adverse clinical features or progressive disease and as part of the standard of care in the community for MDS
- growth factor support
- intensive chemotherapy with, for example, cytarabine, idarubicin, fludarabine or topotecan based regimens
- allogeneic hematopoietic stem cell transplant (which is only available to younger patients who do not have significant co-morbidities and who have a histocompatible donor).

Newer agents include:

- DNA methyltransferase inhibitors i.e. hypomethylating agents such as azacitidine and decitabine (clinical studies have established a role for these agents in both lower and higher risk MDS)
- lenalidomide (for patients with low risk disease, anaemia or changes to chromosome 5)
- agents being tested in clinical trials e.g. tipifarnib, and imatinib.

The only potentially curative treatment for MDS is hematopoietic stem cell transplant (HSCT), however, this is only possible in a small number of patients.

Lower risk MDS

Patients classified as LOW risk\(^10\) according to the IPSS (i.e. INT-1), frequently experience a more indolent course to their disease. Treatment for lower risk patients generally comprises low intensity therapeutic approaches including approved cytotoxic and non-cytotoxic therapies, investigational treatments administered within a clinical trial, and immunomodulatory therapies. Adjuvant supportive care may be used in conjunction with any of these modalities (NCCN, 2009). Hypomethylating agents are indicated for suitable patients, for example patients who are not responsive to growth factor therapy\(^11\) or who are HLA-DR15 negative and of older age. These agents may also be used to reduce tumour

---

\(^7\) IPSS risk categories low and intermediate-1.
\(^8\) To improve haematopoesis and its associated problems of anemia, thrombocytopenia and neutropenia.
\(^9\) IPSS risk categories intermediate-2 and high.
\(^10\) FAB classification refractory anaemia (RA), refractory anaemia with ringed sideroblasts (RARS), and some chronic myelomonocytic leukaemia (CMML) patients.
\(^11\) Usually manifesting as unstable disease including declining cell counts, increased transfusion requirements, and/or repeated infections.
burden (marrow blast count) in patients who have a potential stem cell donor so that they can undergo HSCT.

**Higher risk MDS**

Patients with an IPSS prognosis of INT-2 (HIGH risk)\(^{12}\) have an increase in epigenetic changes with hypermethylation one of the main features of pathogenesis (Saba, 2008). In addition to aggressive cytotoxic therapy, haematopoietic stem cell transplantation and supportive care, low dose hypomethylating agents are indicated for older patients who have a low performance status and co-morbid disease. These patients are not eligible for high dose intensive therapeutic options and currently form the bulk of the patient population treated with hypomethylating agents. These agents are the only approved/licensed drug for patients with higher risks MDS.

**Treatment algorithm**

An MDS treatment algorithm recently agreed in a USA clinical round table (Stone, Sekeres, Garcia-Manero, & Lyons, 2008) and based on National Comprehensive Cancer Network (NCCN) guidelines (NCCN, 2009) is shown in **Figure 3**.

Clinical studies have established a role for hypomethylating agents in both lower and higher risk MDS and hypomethylating agents are indicated in *all* MDS treatment pathways. Lenalidomide is indicated in patients with low risk disease (Figure 3)\(^ {13}\).

---

\(^{12}\) FAB sub-groups include some CMMILs, refractory anaemia with excess blasts (RAEB) and refractory anaemia with excess blasts in transformation (RAEB-T).

\(^{13}\) Lenalidomide is currently the only approved drug for lower risk disease.
Hypomethylating agents in the treatment of myelodysplastic syndromes

Figure 3: Treatment algorithm for MDS based on the NCCN guidelines
Summary

MDS patients are a challenging treatment group. Internationally, treatment options for low risk patients, where the goal of treatment is haematological improvement and an age-appropriate quality of life, low intensity treatment with cytotoxic and non-cytotoxic drugs and adjuvant supportive care may be used; hypomethylating agents are indicated for suitable patients. For higher risk patients, treatment is directed at altering the natural history of the disease to improve survival and delay progression to AML. For this patient population, treatment options include aggressive cytotoxic therapy, haematopoietic stem cell transplantation and supportive care. Low dose hypomethylating agents are indicated for older patients, with low performance status and co-morbid disease who are not eligible for high dose/intensive therapeutic options. This group of patients currently form the bulk of the patient population treated with hypomethylating agents.

Current treatment options for New Zealand patients differ from the model outlined above. Outside of clinical trials, standard treatment comprises transfusion support. A small number of patients are candidates for HSCT, and a small number of patients with low risk disease may be considered for some form of immunomodulatory therapy (e.g. steroids, antithymocyte globulin (ATG)). Currently, New Zealand clinicians do not have access to lenalidomide, growth factors (epo, G-CSF) or hypomethylating agents for these patients.

Assessment of treatment outcomes

Treatment outcomes for MDS are based upon peripheral blood counts and bone marrow evaluation. In addition to complete response and partial response, haematogical response/improvement is an important treatment outcome. The quantitative definition of outcomes in MDS studies has varied in different institutions and over time confounding between-study comparisons.

In response to a request from the FDA to define response criteria in MDS that were associated with improved quality of life (QOL), the International Working Group (IWG) proposed standardised response criteria for evaluating clinically significant responses in MDS (Cheson, et al., 2000). These criteria were updated in 2006 (Cheson, et al., 2006). It is beyond the scope of the current report to detail the various definitions used to report treatment outcome in all MDS studies. However, Table 5 below details the operational definitions used to report key outcomes for the pivotal RCTs of hypomethylating agents reported in this horizon scan.
Table 5: Operational definitions used to report key outcomes in pivotal RCTs of hypomethylating agents

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Phase</th>
<th>RCT</th>
<th>Treatment outcome definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomethylating agent: azacitidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silverman et al. (2002)</td>
<td>III</td>
<td>Randomised controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukaemia group B. (CALGB 9221)</td>
<td>Defined in study</td>
</tr>
<tr>
<td>Silverman et al. (2006)</td>
<td>III</td>
<td>Re analysis of CALGB 9221</td>
<td>IWG 2000 criteria</td>
</tr>
<tr>
<td>Lyons et al. (2009)</td>
<td>II</td>
<td>Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes.</td>
<td>IWG 2000 criteria</td>
</tr>
<tr>
<td>Fenaux et al. (2009)</td>
<td>III</td>
<td>Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study.</td>
<td>IWG 2000 criteria</td>
</tr>
<tr>
<td>Hypomethylating agent: decitabine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kantarjian et al. (2006)</td>
<td>III</td>
<td>Decitabine improves patient outcomes in myelodysplastic syndromes: Results of a phase III randomised study.</td>
<td>IWG 2000 criteria</td>
</tr>
<tr>
<td>Kantarjian et al. (2007)</td>
<td>II</td>
<td>Results of a randomised study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukaemia.</td>
<td>IWG 2000 criteria initially then recoded to IWG 2006 modified criteria</td>
</tr>
<tr>
<td>Wijermains et al. (ASH abstract only) (2008)</td>
<td>III</td>
<td>Low Dose Decitabine Versus Best Supportive Care in Elderly Patients with Intermediate or High Risk MDS Not Eligible for Intensive Chemotherapy: Final Results of the Randomised Phase III Study (06011) of the EORTC Leukaemia and German MDS Study Groups.</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Hypomethylating agents in the treatment of myelodysplastic syndromes
The Comparator

In this report, supportive care is the comparator of choice. All patients diagnosed with MDS receive supportive care to control/treat symptoms associated with anaemia, neutropenia, and thrombocytopenia, improve quality of life and prevent/treat complications. The nature and extent of supportive care varies and depends on a number of factors including the severity of the cytopenias, new developments care standards and the availability of new therapeutic agents.

Internationally, the core elements of supportive care include:

- transfusions (platelets and/or red blood cells) to combat fatigue, dyspnoea and bleeding problems
- antibiotics to treat infections
- growth factors such as granulocyte colony-stimulating factors and recombinant erythropoietin to stimulate the marrow to make more blood cells
- iron chelation therapy to prevent/manage build up of iron in vital organs (Atallah & Garcia-Manero, 2008; Kantarjian, et al., 2006; Saba, 2008)
- The recently published National Comprehensive Cancer Network practice guidelines for MDS (NCCN, 2009) includes detailed guidelines for supportive care in this patient population and adds a number of other dimensions for care of MDS in the community including:
  - observation and clinical monitoring
  - psychosocial support
  - quality of life assessment.

Note: the above comparator may have limited application in New Zealand where:

- supportive care options include transfusions and treatment of infections
- growth factors are not registered or funded for MDS
- while there are a small number of patients on iron chelation, the treatment is difficult and cumbersome for the patient. The oral iron chelator, Exjade®, is registered for this indication in New Zealand but not currently funded. It is funded for MDS patients in Australia.

---

14 NCCN Guidelines for Guidelines for Supportive Care including Adult Cancer Pain, Antiemesis, Cancer-and Chemotherapy-Induced Anemia, Cancer-Related Fatigue, Distress Management, Myeloid Growth Factors, Palliative Care, Prevention and Treatment of Cancer-Related Infections and Senior Adult Oncology

15 Subcutaneous infusion 5-6 nights per week for 5-6 hours, ongoing
Hypomethylating agents in the treatment of myelodysplastic syndromes
The Technology

Hypomethylating agents

Aberrant methylation (hypermethylation) of DNA cytosine residues can silence genes that are essential for the control of normal cell growth and differentiation. MDS is characterised by the hypermethylation/silencing of multiple genes. Hypermethylation may occur early in the disease course and is believed to be associated with disease progression (Solomon, et al., 2008). Hypomethylating agents can reverse this process by inhibiting DNA methyltransferase (DNMT). Azanucleoside DNMT inhibitors 5-aza-2'-deoxycytidine (decitabine) and 5-azacitidine (azacitidine) have been shown to have clinical activity in MDS and leukemic patients (Davisson, 2008).

Azacitidine (5-azacitidine, Vidaza®): is a chemical analogue of cytidine, which is a nucleoside present in DNA and RNA. Azacitidine has at least two mechanisms of action; cytotoxicity at higher doses resulting from incorporation into RNA and DNA, and DNA demethylation at lower doses due to DNMT inhibition. Azacitidine’s inhibition of DNA methylation is responsible for its clinical efficacy in MDS. This inhibition is only seen in dividing cells and occurs in concentrations that do not cause major suppression of DNA synthesis (D’Alo, Voso, & Leone, 2005; Siddiqui & Scott, 2005). It has been reported that a major point in favour of azacitidine is the strong reduction in the proportion of patients that transform to AML (D’Alo, et al., 2005).

Decitabine (5-aza-2’-deoxycytidine, Dacogen®): is a cytosine analogue that distributes extensively throughout human tissue and is also reported to have a dual mode of action depending upon the dose. Decitabine is incorporated into DNA; at high doses it inhibits cell proliferation through non-reversible changes in the DNA, at lower doses it induces hypomethylation. Decitabine treatment has been shown to reverse hypermethylation of cell cycle inhibitory protein p15INK4b which allows the re-establishment of normal p15INK4b protein expression, and has been associated with hematologic response. In theory, decitabine should be more powerful and less toxic than azacitidine.

Stage of development of the technology

In 2000 the FDA awarded decitabine (Dacogen™) orphan drug status16 for use in the treatment of MDS in the USA. In 2003 decitabine was awarded orphan drug status in Europe for the same indication (Wijermans & Lubbert, 2005). In 2006 decitabine was approved in the US for the treatment of all FAB classifications of myelodysplastic syndromes (Gore, Jones, & Kirkpatrick, 2006).

Azacitidine (Vidaza®) was designated as an orphan medicinal product in Europe (EU/3/01/084) in 2002 for treatment of patients with Intermediate-2 and High-risk17 Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukaemia (CMML) who were not eligible for haematopoietic stem cell transplantation. Azacitidine was also designated as an orphan medicinal product EU/3/07/509 on 29 November 2007 for the

---

16 The term orphan drug refers to a pharmaceutical agent that has been developed specifically to treat a rare medical condition (a disease which occurs in less than 200,000 individuals in the USA and less than 5 per 10,000 in Europe). Orphan drug status is designed to encourage drug companies to develop new medications for these diseases.

17 According to the International Prognostic Scoring System (IPSS).
treatment of acute myeloid leukaemia (AML). At the time of orphan medicine designation, CMML was classified as a type of MDS (European Medicines Agency, 2008). In the USA azacitidine (Vidaza®) was approved by the FDA in 2004 for use in the treatment of MDS (Issa, Kantarjian, & Kirkpatrick, 2005; Kaminskas, Farrell, Wang, Sridhara, & Pazdur, 2005) based on the CALGB 9221 study (Silverman, et al., 2002). In 2008 the FDA expanded approval (revised labelling for injection, i.v. or s.c.) for MDS based on data from a large RCT (AZA-001 trial) which demonstrated a significantly improved median overall survival for patients treated with azacitidine and a reduced need for blood transfusions.

Summary
Aberrant methylation of DNA cytosine residues can silence genes that are essential for the control of normal cell growth and differentiation. MDS is characterised by the hypermethylation/silencing of multiple genes. Hypomethylating agents can reverse this process by inhibiting DNA methyltransferase (DNMT). Azanucleoside DNMT inhibitors 5-aza-2'-deoxycytidine (decitabine) and 5-azacitidine (azacitidine) have been shown to have clinical activity in MDS and leukemic patients.

Azacitidine and decitabine have at least two mechanisms of action; cytotoxicity at higher doses resulting from incorporation into RNA or DNA, and DNA demethylation at lower doses due to DNMT inhibition. Inhibition of DNA methylation is responsible for the clinical efficacy of these azanucleosides. Both drugs have been approved for the treatment of MDS in the USA and Europe.

Methods

The search procedure used to identify scientific publications relevant to the questions posed to guide this horizon scan (see page 1) contained the following search terms:

<table>
<thead>
<tr>
<th>Survival benefits</th>
<th>Acute myelogenous leukemia</th>
<th>Leukemia, myeloid, acute malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III study</td>
<td>Leukemia</td>
<td>Methyltransferase</td>
</tr>
<tr>
<td>Randomised</td>
<td>Acute myeloid leukemia</td>
<td>Methyltransferase</td>
</tr>
<tr>
<td>Controlled trial</td>
<td>Azacitadine</td>
<td>Myelodysplastic</td>
</tr>
<tr>
<td>Supportive care</td>
<td>Azacytidine</td>
<td>Myelodysplastic</td>
</tr>
<tr>
<td>Response</td>
<td>Dacogen</td>
<td>Myelodysplastic</td>
</tr>
<tr>
<td>Quality of life (QOL)</td>
<td>Decitabine</td>
<td>Syndrome</td>
</tr>
<tr>
<td>Toxicity profile</td>
<td>Demethylating agent</td>
<td>Myelogenous</td>
</tr>
<tr>
<td>Search terms used:</td>
<td>DNA methylation</td>
<td>Myeloid</td>
</tr>
<tr>
<td>5-aza</td>
<td>Epigenetic therapies</td>
<td>Myelodysplastic</td>
</tr>
<tr>
<td>5-aza-2'-deoxycitidine</td>
<td>Hypomethylating agents</td>
<td>Therapies</td>
</tr>
<tr>
<td>5-Azacitidine</td>
<td>Inhibitor of DNA</td>
<td>Vidaza</td>
</tr>
<tr>
<td>Abnormal methylation</td>
<td>Methyltransferase</td>
<td></td>
</tr>
</tbody>
</table>

The databases searched are listed below:

- All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and N HSEED
- EMBASE - All years 1947-Present with Daily Update
- International Pharmaceutical Abstracts - 1970 to April 2009
- MEDLINE Pending
- Ovid MEDLINE(R) - 1950 to Present with Daily Update

The search procedures developed using the search terms above were tailored to the individual databases searched. No restrictions were placed on the searches. The search procedure and the number of citations identified at each stage are shown in Table 6.
Table 6: Search strategy for hypomethylating agents for MDS

<table>
<thead>
<tr>
<th>Search No</th>
<th>Search terms</th>
<th>No Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp myelodysplastic syndromes/</td>
<td>23351</td>
</tr>
<tr>
<td>2</td>
<td>exp leukemia, Myeloid, Acute/</td>
<td>34657</td>
</tr>
<tr>
<td>3</td>
<td>(&quot;acute myeloid leukemia,&quot; or &quot;acute myelogenous leukemia&quot;).mp. [mp =ti, ab, sh, hw, tn, ot, dm, mf, tx, kw, ct, nm, rw]</td>
<td>29130</td>
</tr>
<tr>
<td>4</td>
<td>1 or 3 or 2</td>
<td>75950</td>
</tr>
<tr>
<td>5</td>
<td>(&quot;Epigenetic therapies&quot; and (&quot;myelodysplastic syndromes&quot; or &quot;leukemia&quot;)).mp. [mp =ti, ab, sh, hw, tn, ot, dm, mf, tx, kw, ct, nm, rw]</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>hypomethylating agents.mp. [mp =ti, ab, sh, hw, tn, ot, dm, mf, tx, kw, ct, nm, rw]</td>
<td>169</td>
</tr>
<tr>
<td>7</td>
<td>(&quot;demethylating agent&quot; and &quot;myeloid malignanc$&quot;).mp. [mp =ti, ab, sh, hw, tn, ot, dm, mf, tx, kw, ct, nm, rw]</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>inhibitor of DNA methyltransferase.mp. [mp =ti, ab, sh, hw, tn, ot, dm, mf, tx, kw, ct, nm, rw]</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>abnormal methylation.mp. [mp =ti, ab, sh, hw, tn, ot, dm, mf, tx, kw, ct, nm, rw]</td>
<td>402</td>
</tr>
<tr>
<td>10</td>
<td>(azacytidine or azacitadine or 5-azacitidine or vidaza or 5-azacitidine or 5-AZA).mp. [mp =ti, ab, sh, hw, tn, ot, dm, mf, tx, kw, ct, nm, rw]</td>
<td>8967</td>
</tr>
<tr>
<td>11</td>
<td>(decitabine or 5-aza-2'-deoxycytidine or dacogen).mp. [mp =ti, ab, sh, hw, tn, ot, dm, mf, tx, kw, ct, nm, rw]</td>
<td>1916</td>
</tr>
<tr>
<td>12</td>
<td>DNA methylation.mp. [mp =ti, ab, sh, hw, tn, ot, dm, mf, tx, kw, ct, nm, rw]</td>
<td>31304</td>
</tr>
<tr>
<td>13</td>
<td>8 or 6 or 11 or 7 or 10 or 9 or 12 or 5</td>
<td>36790</td>
</tr>
<tr>
<td>14</td>
<td>4 and 13</td>
<td>1466</td>
</tr>
<tr>
<td>15</td>
<td>remove duplicates from 14</td>
<td>1124</td>
</tr>
<tr>
<td>16</td>
<td>from 15 keep 1-1016, EMBASE &lt;1980 to 2009 April 27&gt; (802), EMBASE Classic &lt;1947 to 1979&gt; (3), EBM Reviews - Cochrane Central Register of Controlled Trials &lt;1st Quarter 2009&gt; (7), EBM Reviews - Health Technology Assessment &lt;2nd Quarter 2009&gt; (1), Ovid MEDLINE(R) 1950 to Present with Daily Update (203)</td>
<td>1016</td>
</tr>
</tbody>
</table>

A total of 1016 articles were identified for review. The abstracts and/or titles of these articles were assessed for relevance and potential eligibility. Articles were eligible for full text review if they reported on the:

- safety of hypomethylating agents for MDS
- side effects of treatment
- clinical benefit of hypomethylating agents for MDS, outcome improvement in terms of (a) overall survival (OS), (b) time to progression (PFS) or (c) quality of life (QOL).
Following review of the full text of the selected papers articles were shortlisted for reporting. The results of the assessment of these papers are reported below in three separate sections:

- Safety
- Effectiveness
- Quality of life

New and ongoing trials clinical were identified from the metaRegister of Controlled Trials (mRCT)\(^{19}\) and from the ClinicalTrials.gov\(^{20}\) — a registry of federally and privately supported clinical trials conducted in the United States and around the world.

**Previous Horizon Scan reports**

There have been three previous horizon scans of hypomethylating agents (National Horizon Scanning Centre, 2003, 2007, 2008)

- National Horizon Scanning Centre (2008). Decitabine (Dacogen) for myelodysplastic syndrome. University of Birmingham, UK.

These were very brief publications summarising four published phase III randomised controlled trials. They are not reported further.

**Levels of evidence**

There were no systematic reviews (Evidence Level I, Appendix I) of the effectiveness of azacitidine or decitabine in the treatment of MDS.

There were three randomised controlled trials (two Evidence Level II and one at Evidence Level III-1) of the effectiveness of azacitidine therapy in MDS (Appendix B, Tables 9-16).

There were three randomised controlled trials (all Evidence Level II) of the effectiveness of decitabine therapy in MDS (Appendix C, Tables 17-24).

The remaining studies were case series (Evidence Level IV).

Note: the quality of the randomised controlled trials was not assessed.

---

\(^{19}\) [http://www.controlled-trials.com/mrct/]

\(^{20}\) [http://clinicaltrials.gov/]
Hypomethylating agents in the treatment of myelodysplastic syndromes
Clinical Outcomes: Safety

Azacitidine: FDA safety assessment of azacitidine

“Safety evaluation of azacitidine was confounded by the pathophysiology of MDS, which overlaps, to a great extent, with the most common toxicities of azacitidine. Serious adverse events (SAEs) occurred in about 60% of azacitidine-treated patients and in about 36% of observation-arm patients. The most common SAEs resulting in hospitalisation in both arms were thrombocytopenia, febrile neutropenia, fever, and pneumonia. No deaths were attributed to azacitidine. Virtually all (99%) azacitidine-treated patients and over 96% of the observation arm patients reported adverse events. Gastrointestinal events (nausea, vomiting, diarrhoea, constipation, and anorexia), haematologic events (neutropenia, fever, rigors, ecchymoses, and petechiae), injection site events, arthralgia, cough, dyspnea, headache, weakness, dizziness, and insomnia were more commonly reported by patients treated with azacitidine than by patients in the observation arm.

The highest proportion of patients reporting adverse events occurred in the first two cycles of therapy; this proportion decreased in subsequent cycles with the use of appropriate concomitant medications. The most common reasons for azacitidine discontinuation, dose reduction, or therapy interruption (besides the main reason of lack of effectiveness) were neutropenia, leukopenia, and thrombocytopenia. The main indications for concomitant medications to treat adverse events were gastrointestinal symptoms and fever in the azacitidine-treated patients and fever, hypokalaemia, and nausea in observation-arm patients. Blood cell counts were low at baseline in all patients and decreased further in patients treated with azacitidine. Blood cell counts increased in patients who showed responses or improvements. Patients with hepatic or renal impairment were excluded from the clinical trials. Liver function abnormalities occurred, for the most part, in patients with intercurrent illnesses, including hepatobiliary disorders.

More severe abnormalities developed in patients with previously diagnosed liver cirrhosis. In previous literature reports, hepatic coma occurred in patients with extensive metastases to the liver [9]. Renal failure was reported in patients during periods of sepsis and hypotension. Some adverse events, such as vomiting, diarrhoea, headache, injection site erythema, arthralgia, tachycardia, and postprocedural haemorrhage, were reported more frequently by females than males. The proportion of patients with adverse events was not greater in older age groups.”

Since this FDA assessment of azacitidine there have been further randomised trials reporting safety data. In the most recent phase III study of azacitidine treatment of higher risk MDS (Fenaux, et al., 2009), the rate of infections treated with intravenous antimicrobials was significantly higher in the azacitidine group compared with the conventional care group. The most commonly reported grade 3–4 adverse events were peripheral blood cytopenias (Table 7).

21 (Kaminskas, Farrell, Wang, et al., 2005)
22 Hypokalaemia is a condition in which the concentration of potassium in the blood is low.
23 AZA 001 Azacitidine given subcutaneously at 75 mg/m2/d.
Table 7: Grade 3 or 4 haematological toxicity by treatment group

<table>
<thead>
<tr>
<th>Cytopenia</th>
<th>Grade 3 or 4 toxicity‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azacitidine (n=179)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>159 (91%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>149 (85%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>100 (57%)</td>
</tr>
</tbody>
</table>

‡National Cancer Institute’s Common Toxicity Criteria toxicities based on laboratory data

The most common azacitidine related non-haematological adverse event was injection site reaction. Treatment discontinuation before study completion in the azacitidine group was mostly related to haematological adverse events. During the first 3 months of treatment, slightly more deaths occurred in patients in the azacitidine group than in the conventional care group. These deaths were primarily attributed to underlying disease (sepsis or bleeding). Four deaths from cerebral ischaemia in the azacitidine group (two from sepsis and two from bleeding), and one in the conventional care group (receiving low-dose cytarabine) were probably related to treatment.

In a recent phase II randomised trial of three different schedules of azacitidine (Lyons, et al., 2007) there was detailed reporting of grade 3-4 adverse events (Table 8).
### Table 8: Selected grade 3/4 adverse events in patients treated with different dosing regimens of azacitidine who received ≥ 1 dose of azacitidine as of March 31, 2007

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>AZA 5-2-2 (n = 50)</th>
<th>AZA 5-2-5 (n = 48)</th>
<th>AZA 5 (n = 50)</th>
<th>Total (n = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 Adverse Event</td>
<td>38 (78%)</td>
<td>34 (71%)</td>
<td>32 (64%)</td>
<td>105 (71%)</td>
</tr>
<tr>
<td>Hematologic Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (22%)</td>
<td>7 (15%)</td>
<td>7 (14%)</td>
<td>25 (17%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5 (10%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 (40%)</td>
<td>13 (27%)</td>
<td>11 (22%)</td>
<td>44 (30%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (24%)</td>
<td>6 (13%)</td>
<td>7 (14%)</td>
<td>25 (17%)</td>
</tr>
<tr>
<td>Hemorrhagic Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Rectal</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida sepsis</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>AZA=azacitidine.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA-5 = 75 mg/m²/d s.c. for 5 days,  total dose=375 mg/m² per cycle.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA-5-2-2 = 75 mg/m²/d s.c. for 5 days, followed by a 2-day weekend break, followed by 75 mg/m²/d s.c. for 2 days, total dose =525 mg/m² per cycle.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA-5-2-5= 50 mg/m²/d s.c. for 5 days followed by a 2-day weekend break followed by 50 mg/m²/d s.c. for 5 days, total dose =500 mg/m² per cycle.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: (Lyons, et al., 2007)

Lyons et al. (2007) reported that different dosing regimens were generally well tolerated and safety was fairly consistent between the different dosing arms. The majority of treatment-related adverse events (grade 3 or 4) were reported in the first two cycles suggesting that tolerance increased as treatment continued. The most common serious adverse events were anaemia, febrile neutropenia and congestive heart failure: all pre-existent azacitidine treatment. While the safety profiles of the three dose regimens were similar and acceptable, the results of this study suggested that the AZA 5 regimen was better tolerated.
Decitabine: FDA safety assessment of decitabine

The FDA published the following safety assessment in 2006:

- A total of 240 patients with MDS received decitabine (DAC) at the same dose as specified in the three primary studies. DAC was administered in cycles of six weeks, and the median number of cycles was 3, with some patients receiving up to nine cycles.
- There were no deaths that were attributed to DAC toxicity, although thrombocytopenia aggravated by DAC treatment may have contributed to bleeding, including intracerebral haemorrhage. The number of deaths was greater in the supportive care arm than in the DAC treatment arm during the study period; however the total number of deaths during the total observation period was about the same in both arms. Disease progression to AML and infection were the most common cause of death in both arms.
- Haematological adverse events (neutropenia, febrile neutropenia, thrombocytopenia, anaemia and leucopenia) were prominently more common in the DAC arm than in the supportive care (SC) arm. Haematological adverse events did not decrease with successive cycles unless the patient had a response. Gastrointestinal disorders (nausea, constipation, diarrhoea, vomiting, abdominal pain, stomatitis, dyspepsia and ascites) were more common in the DAC arm than in the supportive care arm. They decreased after the first two cycles of DAC therapy with appropriate medications. Fever, bacterial and fungal infections, painful joints or muscles, backaches, chest wall discomfort, headache, insomnia, confusional state, ecchymoses, pallor, erythemas, alopecias and skin disorders were also more common in the DAC arm than in the SC arm. There were no greater than grade 2 hepatic or renal function abnormalities. Vital signs reflected general clinical condition rather than MDS or DAC therapy.
- Adverse events (thrombocytopenia, lymphadenopathy, neutropenia, pneumonia, M. avium infection, cardiac arrest, and elevated liver function tests) led to discontinuation of DAC therapy in 10% of patients, and of withdrawal from the supportive care arm in 2% of patients (because of COPD and dyspnea). About 19% of patients had dose delays, about 5% of patients had dose reduction, and about 11% of patients had dose reductions and dose delay.
- There are no safety data on pregnant or lactating women (who were excluded from enrolment), or on infants and children (MDS is very rare in childhood) in this submission.
- Overdose data is available from older studies in which patients were treated with several fold higher DAC dosages. The main toxicity was haematological.
- The most common adverse events due to DAC overlap with those of MDS making attribution and safety evaluation difficult. DAC therapy is effective in eliminating or reducing transfusion dependence, and the adverse events appear to be tolerable for the achievement of this goal.

Since this FDA assessment of decitabine was reported, there have been further randomised trials reporting safety data. A comparative phase II study comparing three different schedules of low dose decitabine (Kantarjian, et al., 2007) reported that severe (grade 3-4) drug-related extramedullary toxicities were uncommon. Despite repeated courses of therapy (median 6 courses), at the time of reporting 32 (34%) of the 95 patients did not require hospitalisation due to decitabine therapy and there were no deaths directly attributable to decitabine. Myelosupression-associated complications and prolonged myelosupression tended to be

24 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021790s000_Dacogen_MedR.pdf
worse with the 10-day intravenous schedule, as was the incidence of hospitalisation. Most patients received the full decitabine dose schedule.

The most recently completed randomised phase III EORTC trial (06011) of low dose decitabine versus best supportive care in elderly patients (Wijermans, Suciu, et al., 2008) reported greater febrile neutropenia (26% of patients) in the decitabine arm compared to the supportive care arm (7%). Differences in non-haematological toxicities were mainly gastrointestinal. There were slightly more deaths in the decitabine arm (29 patients) than in the supportive care arm (25 patients). Seven deaths were due to progression to AML in the decitabine arm compared to 20 in the supportive care arm, 9 deaths were due to toxicity in the decitabine arm compared to none in the supportive care arm.

Summary

The hypomethylating agents (azacitidine and decitabine), when administered at clinically effective doses, are well tolerated with manageable side effects. The main adverse event associated with the use of these agents is myelosupression including neutropenia, thrombocytopenia and anaemia. Grade 3-4 haematological toxicity generally occurred in <5% of patients in phase III trials. Non-haematological toxicities include nausea, vomiting, diarrhoea, constipation, and injection site reactions. Safety evaluation of these agents may be confounded by the pathophysiology of MDS, which overlaps with the most common toxicities of azanucleosides.
Hypomethylating agents in the treatment of myelodysplastic syndromes
Clinical Outcomes: Effectiveness

Azacitidine

Azacitidine has been assessed in clinical trials for over three decades. The first Investigational New Drug application for azacitidine was submitted by the National Cancer Institute in 1971 for various antineoplastic indications. By 1976 more than 800 patients with AML, chronic myelogenous leukaemia, and various solid tumours had been treated with a variety of azacitidine regimens (von Hoff, Slavick, & Muggia, 1976). At this time, azanucleosides (azacitidine and decitabine) were being developed as cytotoxic drugs. However, their use at intermediate and high doses was limited by prohibitive mucositis and central nervous system (CNS) toxicity.

In 1979 the ability of azacitidine to demethylate newly synthesized DNA and to trigger differentiation of cells was reported (Jones & Taylor, 1980). The clinical development of azacitidine as a hypomethylating agent was initiated by the Cancer and Leukemia Group B (CALGB). Clinical studies of low-dose azacitidine for elderly patients with MDS (who were not eligible for standard chemotherapy), started in the early 1980s and a number of studies were published by the CALGB during the period 1989 to 2002. These studies formed the evidence base for FDA approval of azacitidine in 2002 (Appendix G).

The Cancer and Leukemia Group B (CALGB) trials

Three multicenter CALGB trials and seven single centre trials carried out between 1985 and 2002 documented azacitidine activity in MDS patients. Pharmion Corporation submitted a New Drug Application to the FDA based on the data from three CALGB trials, two single arm phase II studies and one randomised controlled phase III trial. These trials are summarised below and in Appendix H.

In the initial CALGB 8421 phase II study25 (Silverman, et al., 1993), 48 elderly MDS patients with RAEB and RAEB-T received a continuous infusion of azacitidine 75mg/m²/day for 7 days each month. In 43 evaluable patients, the overall response rate was 49%, 5 patients had a complete response (CR). There was a trilineage haematological response in 37% of patients. The median duration of response for patients achieving a complete (CR) or partial (PR) response was 14.7 months. The median survival for all evaluable patients was 13.3 months. The median duration of response and survival was not influenced by age or FAB subtype.

This study was followed by a larger (n=72) multicentre trial (CALGB 8921) with RAEB, RAEB-T and CMML patients treated with a subcutaneous daily bolus of azacitidine at a dose of 75mg/m2/day for 7 days each month (Kaminskas, Farrell, Abraham, et al., 2005; Silverman, et al., 1994). The overall response rate (CR+PR) in the intention-to-treat population was 13.9%. The mean and median total duration of clinical response of PR (or better) for the responders was 565 days (1.5 years) and 117 days, respectively. The median survival times of the responders and of the non-responders were 39.3 and 9.6 months, respectively. The median times-to- transformation to AML of the responders (excluding AML patients) and the non-responders were 59.1 and 21.8 months, respectively. A multicentre randomised controlled trial26 (CALGB 9221) was carried out in 191 elderly MDS patients to...

25 Single arm single centre

26 An open-label, parallel-group, randomised, controlled phase 3 clinical trial (AZA-PH-GL-2003-CL-001 later named AZA-001)
confirm these results (Silverman, et al., 2002). Azacitidine at a dose of 75mg/m^2/day for 7 days each month delivered as a subcutaneous bolus was compared to supportive care alone\textsuperscript{27}. This trial had a crossover design to allow patients treated only with supportive care to cross over to azacitidine after four months if they had disease progression. Treatment with azacitidine was associated with a statistically significantly higher overall response rate (60% vs. 5%, p = 0.0001), longer median time to leukemic transformation or death (21 vs. 13 months, p = 0.007), improved physical function, symptoms, and psychological state for patients initially randomised to azacitidine. The response to azacitidine was independent of the type of MDS.

Patients in the crossover arm (i.e. patients in the supportive care arm who went on to receive azacitidine) had an overall response of 47%. There was a non-significant difference in overall survival with a median survival for azacitidine patients of 20 versus 14 months for patients treated only with supportive care\textsuperscript{28}. The effect of initial treatment with azacitidine on overall survival in this trial was confounded by 49 patients (initially randomised to receive supportive care) who were crossed over to azacitidine during their survival follow-up.

Azacitidine was awarded FDA approval in 2004 based on evidence of (a) improvement in bone marrow function, (b) delayed transformation to AML and (c) improvements in quality of life and survival as demonstrated in the CALB trials \textsuperscript{29}. In the ensuing period, a greater understanding of the biology of myelodysplastic syndromes (Ogata, 2006), the development of new classification and prognostic systems (Greenberg, et al., 1997; Harris, et al., 1999; Kantarjian, et al., 2008) and new response criteria for evaluation of new treatments for MDS (Cheson, et al., 2006) prompted a reanalysis of these data (Kornblith, et al., 2002; Silverman, et al., 2006). Reanalysis validated the previously published results and provided extended safety and quality of life data.

While the early CALGB studies were important in demonstrating the effectiveness of low dose azacitidine in MDS, they had a number of limitations. These included:

- study population heterogeneity
- differences in number of treatment courses delivered
- inconsistencies in the definitions of sub-groups prognosis and outcome
- comparison of patients in all risk groups with supportive care only
- incorporation of patients who changed treatment during the study.

To address these shortcomings, a multicenter, randomised, phase III trial of subcutaneous azacitidine plus best supportive care versus conventional care regimens plus best supportive care for the treatment of MDS, and was initiated between 2003-2007 in Europe. The prime purpose of the study was to determine whether 179 patients with high-risk MDS treated with azacitidine had improved survival compared to patients treated with appropriate conventional care\textsuperscript{30} (n=179). The study also assessed the effect of treatment on response, duration of response, and transformation to acute myeloid leukaemia (AML). Treatment was continued until the end of the study unless there was unacceptable toxicity, relapse after complete or

\textsuperscript{27} Supportive care was given to all patients; the supportive care group received no other treatment.

\textsuperscript{28} There are variations in the figures reported in early and later retrospective reanalysis of these data as a result of classification changes.


\textsuperscript{30} Conventional care included best supportive care (n=105), low dose cytarabine (n=49) and intensive chemotherapy (n=25).
partial response, transformation to AML or disease progression. The study flow chart is shown in Figure 4.
Azacitidine was administered for a median of 9 cycles (range 1 to 39), best supportive care was administered for a median of 7 cycles (range 1 to 26). In the low dose cytarabine arm therapy was administered for a median of 4.5 cycles (range 1 to 15), and in the chemotherapy with cytarabine and anthracycline arm for a median of 1 cycle (range 1 to 3, i.e. induction plus 1 or 2 consolidation cycles). Eighty-six percent of patients treated with azacitidine remained on the initial dose of 75 mg/m$^2$ per day throughout the study.

The hazard ratio for overall survival of patients treated with azacitidine was 0.58 (95% CI 0.43–0.77) with 82 azacitidine deaths compared to 113 for patients treated with conventional care regimens. Kaplan-Meier survival curves (Figure 5) for the azacitidine and conventional care groups separated permanently after about 3 months, at which time 140 (78%) of 179 patients receiving azacitidine had completed 3 cycles of treatment. After a median follow-up of 21.1 months (interquartile range 15.1-26.9) the median overall survival was 24.4 months in the azacitidine group compared with 15 months in the conventional care group (difference of 9.4 months, p = 0.0001); this varied from median survival not reached at 35 months in good prognosis patients, to a median of 17.2 months in poor prognosis patients (Figure 5).

The median time to transformation to AML was significantly longer in the azacitidine group (17.8 vs. 11.5 months, hazard ratio = 0.50, p< 0.0001). Remission rates (CR+PR 29% vs. 17.8 vs. 11.5 months, hazard ratio = 0.50, p< 0.0001). Remission rates (CR+PR 29% vs.
Hypomethylating agents in the treatment of myelodysplastic syndromes

12%, \( p = 0.0001 \)), haematological improvement rates (49% vs. 29%, \( p < 0.0001 \)) median time to disease progression, relapse or death (14.1 vs. 8.8, \( p = 0.047 \)) and the median duration of haematological response were also significantly longer in the azacitidine group (13.6 vs. 5.2 months, \( p = 0.0002 \)).

![Kaplan-Meier survival curves for patients with MDS treated with azacitidine or conventional care](image)

Source: (Fenaux, et al., 2009)

**Figure 5:** Kaplan-Meier survival curves for patients with MDS treated with azacitidine or conventional care

The proportion of patients, who were dependent upon RBC transfusion at the start of the study, that became transfusion independent during the study, was higher in the azacitidine group than the conventional care group (45% vs. 11.4 %, \( p < 0.0001 \)). The analysis of predefined sub-groups showed consistently superior responses in patients treated with azacitidine compared to those receiving conventional care (Appendix D). Of particular significance was the benefit derived by patients with alterations in chromosome 7.

**Community dosing schedules**

The standard schedule of 75mg/m\(^2\) administered subcutaneously or intravenously daily for seven days every 4 weeks (Fenaux, et al., 2009) may be relatively inconvenient for patients, pharmacists, nurses and doctors. Lyons et al. (2009) recently published the results of a multicentre, community-based randomised phase II study to evaluate three different schedules for azacitidine which avoided weekends and allowed for long term ambulatory therapy (Figure 6). Only 30% of patients in this study had higher risk MDS, reflecting the distribution of patients in the community setting.
The three dosage schedules evaluated by Lyons et al. (2009) were:

- **AZA-5**  
  75 mg/m²/d s.c. for 5 days, total dose = 375 mg/m² per cycle

- **AZA-5-2-2**  
  75 mg/m²/d s.c. for 5 days, followed by a 2-day weekend break followed by 75 mg/m²/d s.c. for 2 days, total dose = 525 mg/m² per cycle

- **AZA-5-2-5**  
  50 mg/m²/d s.c. for 5 days followed by a 2-day weekend break followed by 50 mg/m²/d s.c. for 5 days, total dose = 500 mg/m² per cycle

The FDA approved regimen of 75 mg/m²/d s.c. for 7 days, total dose = 575 mg/m² per cycle (Fenaux, et al., 2009) was *not included* in the study.

---

<table>
<thead>
<tr>
<th>Screening</th>
<th>Cycle 1</th>
<th>Cycles 2-5</th>
<th>Cycles 7-18</th>
<th>End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days -21 to -1</td>
<td>AZA 5-2-2</td>
<td>Repeat cycle every 4 weeks</td>
<td>Maintenance Randomization</td>
<td>4 weeks after last dose</td>
</tr>
<tr>
<td>Days 1-9</td>
<td>AZA 5-2-5</td>
<td>AZA 5</td>
<td>q 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Days 1-12</td>
<td>AZA 5</td>
<td>AZA 5</td>
<td>q 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**AZA=azacitidine, IWG=International Working Group**

Source: (Lyons & Cosgriff, 2009)

**Figure 6:** *Study design used by Lyons and Cosgriff (2009) to evaluate three different schedules for azacitidine in a community setting*

A total of 151 *primarily lower risk MDS* patients were randomised with approximately 50 patients allocated to each treatment group. Haematological improvement was achieved in 44% of the 7-day (AZA 5-2-2), 45% of the 10-day (AZA-5-2-5) and 56% of the 5-day (AZA-5) study arms. The proportion of transfusion dependent patients who achieved independence ranged from 55%-64% in the three arms with the highest score achieved by the AZA-5 dosing arm.

These 3 alternative azacitidine dosing regimens provided comparable results consistent with those previously reported with the approved azacitidine dosing schedule. Each of the 3 alternative dosing regimens of azacitidine was tolerable, with similar safety profiles to that observed with the approved dose. In this study the improvements observed with each of the schedules was similar, however, the results suggested that the 5-day regimen (AZA-5, ) *may*...
be better tolerated, with a lower more convenient dosing schedule than the 7-day (AZA 5-2-2) or 10-day (AZA-5-2-5) schedule.

New developments and ongoing clinical trials

In an attempt to increase the CR rate in patients (traditionally required for improved survival in cytotoxic therapy) there have been a number of studies of azacitidine in combination with agents with a different mechanism of action including all-trans retinoic acid (ATRA), histone deacetylase inhibitors (HDAC) such as valproic acid (Soriano, Yang et al. 2007) MS-275, farnesyltransferase inhibitors such as tipifarnib, and 5q31 clone inhibitors such as lenalidomide (Gore, 2005; Gore, Baylin, et al., 2006; Gore & Hermes-DeSantis, 2008; Sekeres, 2008; Soriano, et al., 2007).

In 2007 the Australasian Leukaemia and Lymphoma Group registered a new phase I/II trial to determine the safety and efficacy of 5-azacitidine (Vidaza) and thalidomide combination therapy in patients with myelodysplastic syndromes (MDS). Gore et al. (2008) reported that 16 phase I-III studies of azacitidine therapy combinations were under investigation. Recruiting clinical trials identified for this report (Appendix E) revealed an ongoing interest in the development of combination therapy including azacitidine. Other developments of interest include investigations of the clinical utility of:

- oral azacitidine (Garcia-Manero, Stoltz, Ward, Kantarjian, & Sharma, 2008)
- azacitidine prior to allogeneic stem cell transplant (high risk MDS)
- azacitidine in relapsing patients
- azacitidine maintenance therapy.

Decitabine

Decitabine has been evaluated in clinical trials for over two decades. It was initially developed as a classical anti-tumour agent. Early phase I studies established the maximum tolerated dose (MTD) as 1500-2250 mg/m² in patients with acute leukaemia (Momparler, Rivard, & Gyger, 1985; Rivard, et al., 1981). The dose-limiting toxicity was primarily myelosupression. In these early trials decitabine was utilised in a similar way to its structural relative cytarabine (ARA-C). Decitabine showed no advantage over ARA-C and had a poor toxicity profile. Its development as a cytotoxic drug was halted. With the discovery of the hypomethylating activity of low doses of azanucleosides (i.e. doses 5-20 times lower than the MTD) and advances in the understanding of the nature of MDS, there was a renewed interest in decitabine.

Clinical studies forming the basis for FDA approval

The initial studies of hypomethylating activity of decitabine in patients with MDS were conducted in Europe by the European Organisation for Research and Treatment of Cancer (EORTC). Key phase II studies were published in 1997 and 2000 (Wijermans, Krulder, Huijgens, & Neve, 1997; Wijermans, et al., 2000).

Wiermans et al. (1997) in a single centre open label, single arm phase II trial (PCH-91-01) examined the effect of low-dose decitabine in 29 elderly patients with high risk MDS. Decitabine was administered at low doses (135 mg/m² total dose/course) by continuous

infusion over a 72 hour period. Trilineage responses were observed in these patients with an overall response rate of 54% and a CR rate of 28%. The median overall survival was 46 weeks.

To confirm these findings a second, larger, multi-centre phase II study was carried by Wijer man et al. (2000) in 66 elderly patients with a median age of 68 years. Patients received 45 mg/m^2 of decitabine for 3 days (135 mg/m^2 total dose/course) every 6 weeks for a maximum of 6 cycles. Patients who achieved a CR after 2 courses received an additional 2 cycles of consolidation therapy. Endpoints were response rate, toxicity, response duration, survival from the start of therapy and overall survival. The overall response rate was 49% (32 cases, 95% CI 38-63%), for high-risk patients. The response rate 64% (16 of 25 cases) was higher for patients achieving either a PR or CR. The response duration was 39 weeks (95% CI 25-47 weeks) and 36 weeks (95% CI 25-47 weeks) respectively. The median progression free survival\(^{33}\) was 25 weeks (95% CI 4-84 weeks). The median survival from the start of therapy was 15 months (95% CI 13.3-16.7 months) and from the date of diagnosis was 22 months (95% CI 14.2-29.8 months). A notable finding was an early observed increase in platelet counts\(^{34}\).

The results of these Phase II studies together with a third phase II study (PCH-97-19, n = 75) of MDS in an elderly population were reported as a pooled analysis in 2002 (Wijermans, Luebert, & Verhoef) and again in 2005 with the addition of patients from a US phase II study (PCH-95-06) (Wijermans & Lubbert). The pooled odds rate ratio (ORR) was 49%, haematological improvement (HI) 14% and median overall survival (OS) 15 months; the 2 year survival in this population was 34%. A significant correlation was reported between OS and age < 65 years, IPSS score and low risk cytogenetics.

The promising results of these phase II studies led to a multi-institutional, Phase III randomised trial (D0007) of decitabine plus supportive care versus supportive care alone in 170 patients (Kantarjian, et al., 2006). Adult patients with de novo or secondary MDS with any FAB classification and INT-1, INT-2 and HIGH IPSS risk groups were eligible for this pivotal study. Patients with a diagnosis of AML (≥ 30% blasts) or other progressive malignant disease were excluded. Cases were stratified by IPSS risk group. Decitabine was administered intravenously over 3 hours at a dose of 15 mg/m^2 every 8 hours for 3 days: this cycle was repeated every 6 weeks (dependent upon recovery from myelosuppression).

Supportive care was administered in both arms according to “generally accepted guidelines” and included RBC and platelet transfusion, with hematopoietic-CSF as indicated. Therapy was discontinued after 2 cycles of a maintained CR. Quality of life (QOL) was assessed at baseline and at the end of each treatment cycle. The results of this trial are summarised below and in Appendix C.

The overall response rate (PR+CR, 7+8 cases) for decitabine was 17% (15 cases) compared with 0% for supportive care alone (p< 0.001). All responses were durable (median 10.3 months, range 4.1-13.9 months). Haematological improvement was observed in 13% of decitabine patients and 7% of patients receiving only supportive care (p< 0.001).

Responses were observed across all IPSS risk groups and similar response rates were observed in patients with de novo and secondary MDS. Patients treated with decitabine had a

\(^{33}\) Defined in this study as a deterioration of blood counts leading to increased transfusion requirements, or an increase in the number of myeloblasts by more than 10%.

\(^{34}\) This phenomenon was investigated subsequently by
longer median survival (12.1 vs. 7.8 months, time to AML or death) but the trend was not significant ($p = 0.16$) (Figure 7A).

Sub-group analysis indicated significant survival advantages in patients with higher IPSS risk scores ($p< 0.3$, $p = 0.01$) and de novo MDS ($p<.04$), see Figures 7B and 7C. The supportive care arm had an approximately 2-fold increased risk of AML progression or death ($HS = 0.580$, 95% CI 0.37-0.91). The median number of courses of decitabine given was 3 (range 0-9).

Decitabine resulted in a statistically superior quality of life compared with best supportive care alone in global health status ($p< 0.05$), fatigue ($p< 0.05$) and dyspnea ($p< 0.05$). Decitabine was well tolerated with a manageable toxicity profile. Fewer patients died in the decitabine arm (14% vs. 22%). Serious adverse events were greater in the decitabine than the supportive care alone arm (69% vs. 56%). The most common adverse events in both arms were neutropenia, thrombocytopenia, anaemia, febrile neutropenia and leukopenia.

Figure 7A: Time to AML or death for all patients treated with decitabine versus supportive care
Figure 7B: Time to AML or death for treatment naive patients treated with decitabine or supportive care

Figure 7C: Time to AML or death for IPSS INT-2 and high-risk patients treated with decitabine or supportive care

The foregoing studies formed the basis for the FDA approval in 2000 and 2003 of decitabine for all FAB subgroups. In addition there have been a number of significant post-approval studies in response to (a) questions about the optimal dosage and scheduling of decitabine, (b) advances in the understanding of its mechanism of action, (c) experience with responding phase II patients after disease recurrence and (d) changes in the classification status of CMML.

Post FDA approval studies
A phase II, randomised, open label study (Kantarjian, et al., 2007) compared three different schedules of low dose decitabine in 95 higher risk MDS patients (including patients with
Hypomethylating agents in the treatment of myelodysplastic syndromes

A total dose of 100 mg/m² was delivered as 10 mg/m² i.v. over 1 hour daily for 10 days, 20 mg/m² i.v. over 1 hour daily for 5 days, 20 mg/m² s.c. twice daily for 5 days. Courses were administered every 4 weeks.

In an adaptive randomisation design, after the 45th case, patients were preferentially randomised to the arm with the higher CR rate. Overall 73% of patients had an objective response according to modified IWG criteria (Cheson, et al., 2006). The schedule with the highest dose intensity (i.e. the 5-day i.v. schedule) was reported to be the more effective schedule. The original 3-day schedule used in the pivotal phase III RCT was not included and the Bayesian trial design has not been universally accepted (Ruter, Wijermans, & Lubbert, 2006).

Ruter et al. (2006) reported the results of the retreatment of 22 elderly patients (median age 71 years), who had initial treatment with low dose decitabine in earlier phase II trials. These patients received 15 mg/m² over 4 hours, 3 times per day on 3 consecutive days with a total dose of 135 mg/m² repeated every 6 weeks. After a median of 3 courses (range 1-6 courses), administered a median of 11 months after the initial treatment, ten (45%) patients had objective responses. The quality and duration of the second remissions were reported to be inferior and the authors concluded that decitabine responsive patients might benefit from continuation of the initial treatment.

Decitabine has also been shown to be effective in patients with chromosome 7 abnormalities, which carries a poor prognosis. Following a reanalysis of data for azacitidine, Ruter et al. (2007) suggested that this may be considered to be a “class effect” (Ruter, et al., 2007).

A review of the treatment effectiveness of 31 CMML (WHO criteria) patients treated in three phase II trials was carried out by Wijermans et al. (2008) at a total dose of 135 mg/m² administered over 3 days. The ORR was 25% and a haematological improvement was observed in 11% of patients.

In 2008 the results of the phase III EORTC 06011 randomised trial of low dose decitabine versus best supportive care in 233 elderly patients with intermediate or high risk MDS (Wijermans, Suciu, et al., 2008) was reported in an abstract. In this trial patients were randomised to either supportive care or a decitabine schedule of 15 mg/m² i.v. over 4 hours every 8 hours for the first 3 three consecutive days of every 6 week-cycle, for a maximum of 8 cycles. The overall response rate was 34% in the decitabine arm and 2% in the supportive care arm. The median overall survival was 0.84 for decitabine versus 0.71 years for supportive care. The progression free survival was longer in patients treated with decitabine (median 0.55 versus 0.25 years, p = 0.004). Time to AML or death was not significantly improved (p = 0.24). The number of treatment cycles was limited in this study.

New developments and ongoing clinical trials

It has been reported that the future use of decitabine is likely to be in combination with other therapies. Decitabine may be combined to augment its epigenetic effect. Combinations of decitabine and histone deacetylase (HDAC) inhibitors are synergistic in reactivating gene expression. Trials combining decitabine with valproic acid (VPA), vorinostat, depsipeptide, and HDAC inhibitors are ongoing (Jabbour, Issa, Garcia-Manero, & Kantarjian, 2008).

35 PCH 91-01, PCH 95-11, PCH 97-19.
36 PCH 91-01, PCH 95-11, PCH 97-19.
Other agents that are being studied in combination with decitabine include amsacrine, idarubicin, daunorubicin, topotecan, cisplatin, carboplatin and imatinib (Saba, 2008). Recruiting trials involving these and other newer agents are listed in Appendix F.

A phase I/II study (Soriano, Yang et al. 2007) of the combination of 5-azacitidine (5-AZA), valproic acid (VPA), and ATRA in patients with acute myeloid leukaemia or high-risk myelodysplastic syndrome concluded that the combination was safe and had significant clinical activity.

Fifteen active trials of decitabine in MDS are currently registered with the NCI (Appendix F).
Clinical Outcomes: Quality of Life

Myelodysplastic syndromes differ from many other hematologic malignancies in their chronicity (often without disease progression to AML) and in the morbidity and mortality caused by recurring cytopenias. Alleviation of disease-related complications and improved quality of life (QOL) are important goals of therapy (Cheson, et al., 2000).

Supportive care including long-term transfusion support for patients is complicated by required premedication, development of antibodies to red blood cells (RBCs), febrile or allergic reactions, transmission of infectious agents (Gupta, LeRoy, Luikart, Bateman, & Morrison, 1999), and the longterm complication of iron overload from transfusion support which is a significant cost to the health service.

Thus, reducing transfusion dependency and normalising cytopenias and their associated complications to enhance overall quality of life in patients with MDS (Lyons, et al., 2007) is an important endpoint/outcome. The importance of quality of life assessment in the evaluation of therapeutic intervention is emphasised in the NCCN clinical practice guidelines for MDS (NCCN, 2009). Two of the three phase III RCTs reviewed in this report included a quality of life assessment.

Azacitidine

Kornblith et al. (2002) reported on the impact of azacitidine on the quality of life of 191 patients with MDS assessed in the randomised phase III Cancer and Leukemia Group B trial (9221). All FAB sub-types were included and quality of life was assessed by centrally conducted telephone interviews at baseline and days 50, 106, and 182. Overall quality of life, psychological state, and social functioning were assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C3037, and the Mental Health Inventory (MHI)38. Patients receiving best supportive care only, tended to show a decrease in overall QOL scores in the range of 5.2-8.1 points while patients treated with azacitidine showed QOL score increments in the range 7.7-19.3 points.

Patients receiving azacitidine experienced significantly greater improvement in:

- fatigue (EORTC, p = 0.001)
- dyspnea (EORTC, p = 0.0014)
- physical functioning (EORTC, p = 0.002)
- positive effect (MHI, p = 0.0077)
- psychological distress (MHI, p = 0.015).

The authors concluded that azacitidine not only effectively produces a partial or complete regression in MDS but also and improves the patient’s quality of life.

Decitabine

Kantarjlan et al. (2006) reported on the impact of decitabine therapy on the quality of life of patients with MDS assessed in a randomised phase III trial. QOL was assessed for all FAB sub-types at baseline, at the end of each dosing cycle, and at the end of treatment using the

37 http://groups.eortc.be/qol/qolg_activities.htm
EORTC QLQ C30 (versions 1.0 and 3.0)\(^{39}\). Scores were computed according to EORTC standards\(^{40}\). Decitabine resulted in a statistically superior QOL compared with best supportive care in several QOL parameters. Improvements in global health status \((p = 0.05\) at the end of cycles 2 and 4\), fatigue \((p = 0.05\) at the end of cycles 2, 4, 5, and 6\), and dyspnea \((p = 0.05\) at the end of all 6 cycles\) were sustainable effects observed during decitabine treatment.

### Summary

MDS severely affects the patient’s quality of life and, until recently, available treatments, particularly for the older patients, have been very limited. Hypomethylating agents (azacitidine and decitabine) have shown survival benefit in clinical trials in these patients. Promising (though relatively low) response rates in early phase II trials in both agents led to the initiating of randomised controlled trials designed to confirm the phase II studies response rates and establish if treatment with these agents conferred a survival advantage and/or delayed progression to AML. The key features of these trials were the achievement of:

- durable response rates
- delayed time to progression to AML
- a manageable toxicity profile.

Clinical trials in this area are still ongoing, and preliminary data indicate for the first time that the natural history of MDS may be changed by a non-intensive treatment, characterised by an outstanding toxicity profile (Leone, Voso, Teofili, & Lubbert, 2003). However, morphologic evidence of disease rarely disappears with treatment and several courses may be needed for best response.

While approval from the FDA for the use of these agents has been obtained for all FAB sub-types of MDS the best responses have been demonstrated in patients with:

- poor prognosis disease e.g. patients with chromosome 7 irregularities
- older age
- AML by newer classifications (20-30% blasts).

Treatment with the hypomethylating agents (azacitidine and decitabine) has also resulted in a substantially improved quality of life coupled with reduced reliance on transfusions and delayed time to transformation to AML. Particular improvements were reported in overall health status, fatigue, dyspnea and psychological state.

---

\(^{39}\) [http://groups.eortc.be/qol/qolg_activities.htm](http://groups.eortc.be/qol/qolg_activities.htm)

\(^{40}\) Published in the third edition of the EORTC QLQ-C30 scoring manual
Potential Cost Impact

The FDA recently approved several drugs for treating MDS, including azacitidine and decitabine, lenalidomide, and deferasirox (Exjade®, a new oral iron chelator). The development of these novel therapeutic agents for MDS has substantially increased clinical implications and treatment costs for these patients as they need to be given monthly over a prolonged period of time to be effective.

Treatment with immunosuppressive therapy has been therapeutically beneficial for a subset of younger patients with MDS. Because the economic impact of these therapies are substantial and have received only limited attention, Greenberg et al. (2008) examined the costs of drugs used to treat myelodysplastic syndromes. In this article the authors evaluate the costs of specific drugs and their sequential use in the lower-risk IPSS (low and intermediate-1) subgroups based on the NCCN guidelines. Results estimated an average annual cost for potentially anaemia-altering drugs of $63,577 per patient (range $26,000 to $95,000, depending on the specific therapies). In patients for whom the therapies failed, annual costs for iron chelation plus red blood cell transfusions was estimated to average $41,412. This article suggests that the economic impact of drug therapy should be weighed against the patient’s potential for improvement in clinical outcomes, quality of life, and transfusion requirements (Greenberg, et al., 2008).
Hypomethylating agents in the treatment of myelodysplastic syndromes
Ethical Considerations

No special ethical considerations arising from the use of this technology were identified.
Hypomethylating agents in the treatment of myelodysplastic syndromes
Training and Accreditation

Treatment guidelines

Evidence-based treatment guidelines for the use of these therapies in MDS have been produced in Britain (Bowen, et al., 2003), the USA (Saba, 2007) and Italy (Alessandrino, et al., 2002; Bernasconi, et al., 2007; Greenberg, et al., 2006; Greenberg, et al., 2008; NCCN, 2009). The most recent USA guideline (NCCN, 2009) uses the FAB and WHO classifications for MDS, the IPSS for prognostic stratification.
Hypomethylating agents in the treatment of myelodysplastic syndromes
Limitations of the Assessment

A quality assessment of the reported studies was not made. There are quality and comparability issue between studies (and in particular the early and later studies) that have not been addressed by this horizon scan. They include:

- blinding of study participants and the study doctors
- response criteria issues
- pathology review
- trial design
- data auditing and protocol compliance
- supportive care
- blood and marrow examination timing variations.

There are also issues relating to multiple analyses and reanalysis of the original data that formed the basis for the FDA and EMEA approvals of azacitidine and decitabine to accommodate new disease classifications and definitions of response and outcome. This has led to slight variations in the responses reported in different publications and summaries.
Hypomethylating agents in the treatment of myelodysplastic syndromes
References


Garcia-Manero, G. (2008). All MDS patients are not the same. *Clinical Advances in Hematology and Oncology, 6*(12), S8-S10.


Hypomethylating agents in the treatment of myelodysplastic syndromes


Hypomethylating agents in the treatment of myelodysplastic syndromes


Hypomethylating agents in the treatment of myelodysplastic syndromes
Appendix A: International Working Group (IWG) Response Criteria

Altering disease natural history

Complete remission (CR)
- Bone marrow evaluation: Repeat bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines.* When erythroid precursors constitute less than 50% of bone marrow nucleated cells, the percentage of blasts is based on all nucleated cells; when there are 50% or more erythroid cells, the percentage blasts should be based on the nonerythroid cells.
- Peripheral blood evaluation†: Hemoglobin greater than 11 g/dL (untransfused, patient not on erythropoietin) Neutrophils 1500/mm³ or more (not on a myeloid growth factor) Platelets 100 000/mm³ or more (not on thrombopoietic agent) Blasts, 0%.

Partial remission (PR)
All the CR criteria (if abnormal before treatment), except:
- Bone marrow evaluation: Blasts decreased by 50% or more over pre-treatment, or a less advanced MDS FAB classification than pre-treatment. Cellularity and morphology are not relevant.

Stable disease
- Failure to achieve at least a PR, but with no evidence of progression for at least 2 months.

Failure
- Death during treatment or disease progression characterised by worsening of cytopenias, increase in the percentage bone marrow blasts, or progression to an MDS FAB subtype more advanced than pre-treatment.

Relapse after CR or PR (one or more of the following)
- Return to pre-treatment bone marrow blast percentage.
- Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets.
- Reduction in hemoglobin concentration by at least 2 g/dL or transfusion dependence.

Disease progression
- For patients with less than 5% blasts: a 50% or more increase in blasts to more than 5% blasts.
- For patients with 5% to 10% blasts: a 50% or more increase to more than 10% blasts.
- For patients with 10% to 20% blasts: a 50% or more increase to more than 20% blasts.
- For patients with 20% to 30% blasts: a 50% or more increase to more than 30% blasts.

One or more of the following:
- ≥50% decrement from maximum remission/response levels in granulocytes or platelets,
- reduction in hemoglobin concentration by at least 2 g/dL,
- transfusion dependence.
Disease transformation
- Transformation to AML (30% or more blasts).

Survival and progression-free survival

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Response category</th>
<th>Definition</th>
<th>Point of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>All patients</td>
<td>Death from any cause</td>
<td>Entity into trial</td>
</tr>
<tr>
<td>Event-free survival</td>
<td>All patients*</td>
<td>Failure or death from any cause</td>
<td>Entity into trial</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>All patients</td>
<td>Disease progression or death from MDS</td>
<td>Entity into trial</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>CR</td>
<td>Time to relapse</td>
<td>First documentation</td>
</tr>
<tr>
<td>Cause-specific death</td>
<td>All patients</td>
<td>Death related to MDS</td>
<td>Death</td>
</tr>
</tbody>
</table>

IPSS should be used as the primary stratiﬁcation. Complete blood counts should be evaluated at least monthly, or more often if clinically indicated, to establish the durability of responses.
*Under circumstances in which presentation of event-free survival may be appropriate for responders only, this point should be clearly stated.

Cytogenetic response
- Major: No detectable cytogenetic abnormality, if pre-existing abnormality was present.
- Minor: 50% or more reduction in abnormal metaphases.
- Fluorescent in situ hybridization may be used as a supplement to follow a speciﬁcally deﬁned cytogenetic abnormality.

Quality of life
- Measured by an instrument such as the FACT Questionnaire.
- Clinically useful improvement in speciﬁc domains: Physical Functional Emotional Social Spiritual

Hematologic improvement (HI)
- Improvements must last at least 2 months in the absence of ongoing cytotoxic therapy. Hematologic improvement should be described by the number of individual, positively affected cell lines (e.g., HI-E; HI-E 1 HI-N; HI-E 1 HI-P 1 HI-N).

Erythroid response (HI-E)
- Major response: For patients with pretreatment hemoglobin less than 11 g/dL, greater than 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients.
- Transfusion independence.
- Minor response: For patients with pretreatment hemoglobin less than 11 g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, 50% decrease in transfusion requirements.

41 Requires 20 analysable metaphases using conventional cytogenetic techniques.
Platelet response (HI-P)
- Major response: For patients with a pretreatment platelet count less than 100 000/mm³, an absolute increase of 30 000/mm³ or more; for platelet transfusion-dependent patients, stabilisation of platelet counts and platelet transfusion independence.
- Minor response: For patients with a pretreatment platelet count less than 100 000/mm³, a 50% or more increase in platelet count with a net increase greater than 10 000/mm³ but less than 30 000/mm³.

Neutrophil Response (HI-N)
- Major response: For absolute neutrophil count (ANC) less than 1500/mm³ before therapy, at least a 100% increase, or an absolute increase of more than 500/mm³, whichever is greater.
- Minor response: For ANC less than 1500/mm³ before therapy, ANC increase of at least 100%, but absolute increase less than 500/mm³.

Progression/relapse after HI
One or more of the following:
- A 50% or greater decrement from maximum response levels in granulocytes or platelets.
- A reduction in hemoglobin concentration by at least 2 g/dL, or transfusion dependence.
- Notes: for a designated response (CR, PR, HI), all relevant response criteria must be noted on at least 2 successive determinations at least 1 week apart after an appropriate period following therapy (e.g. 1 month or longer).
Hypomethylating agents in the treatment of myelodysplastic syndromes
### Appendix B: Azacitidine Evidence Tables

#### Table 9: Silverman et al (1993)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study Study size</th>
<th>Population</th>
<th>Azacitidine dose/ schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverman (1993)</td>
<td>Phase II Single arm CALGB 8421, n=49 (1 withdrawn prior to treatment, 43 evaluable)</td>
<td>Male=31 Female=17 Median age=65 yrs (range 35-81 yrs) RAEB =23 RAEB-T=24 AML=1</td>
<td>Intravenous continuous infusion 75mg/m²/day for 7 days every 4 weeks Total dose =525mg/m²</td>
<td>Response rate (CR+PR+HI)=49% Median remission duration=14.7 months Median survival =13.3 months Not evaluable=5 Complete response=5(12%) Partial response=11(25%) Haematological improvement=5(12%) Total responses =21(49%) Trilineage response=16(37%) Best response after a median of 3.8 courses (range 2-11)</td>
<td>Myelosupression or Cytopenia requiring dose modification in 33% of patients. Mild to moderate nausea and/or vomiting 63% of patients.</td>
<td>The results of this trial establish azacitidine as an active agent in RAEB and RAEB-T. Further studies have been initiated to explore other doses and schedules in an ambulatory setting.</td>
</tr>
</tbody>
</table>
### Table 10: Silverman et al. (1994)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study Study size</th>
<th>Population</th>
<th>Azacitidine dose/ schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverman (1994)</td>
<td>Phase II Single arm</td>
<td>Male=47 Female=23 Median age= 66 yrs (range 23-82 yrs) RA=7 RARS=4 RAEB=19 RAEB-T=16 CMML=14 AML=10</td>
<td>Subcuraneous 75mg/m² /day for 7 days every 4 weeks (ambulatory) Total dose=525mg/m²²</td>
<td>Response rate=53% Median response duration=17.3 months Not evaluable=4 Complete response=8(12%) Partial response=10(15%) Haematological improvement=18(27%)</td>
<td>Nausea and vomiting =83% mostly mild.</td>
<td>The activity of azacitidine administered i.v. or s.c. is comparable at the dose and schedule tested.</td>
</tr>
<tr>
<td>Evidence level §IV USA</td>
<td>CALGB 8921 n=72(68 evaluable)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publication</td>
<td>Type of study</td>
<td>Study size</td>
<td>Population</td>
<td>Azacitidine dose/ schedule</td>
<td>Response</td>
<td>Toxicity</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>------------</td>
<td>------------</td>
<td>-----------------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Silverman (2002)</td>
<td>Randomised Crossover</td>
<td>CALGB 9221 n=191</td>
<td>Male=132 Female=59 Median age= 68 yrs (range 31-92 yrs) All 5 MDS subtypes IPSS LOW=7 IPSS INT-1=37 IPSS INT-2=22 IPSS HIGH=15</td>
<td>Azacitidine (AZA) n=99 (+best supportive care) Subcutaneous 5mg/m²/day for 7 days every 4 weeks. Total dose=525mg/m²</td>
<td>Follow-up= 54 months/ until death Response rate= AZA 60% vs. SC 5% p=0.0001. Complete response=AZA 7% vs. SC 0% p=0.01. Partial response=AZA 16% vs. SC 0% p</td>
<td>Myelosupression Cytopenia AZA grade 3 or 4 toxicity leukopenia = 59%, granulocytopenia =81%, thrombocytopenia =70% Toxicity was transient, and patients usually recovered in time for the next treatment cycle. Infection was thought to have been related to treatment in 20% of patients. Nausea or vomiting occurred in 4%. There was one (&lt;=1%) treatment-related death. Aza C treatment results in significantly higher response rates, improved quality of life, reduced risk of leukemic transformation, and improved survival compared with supportive care. Aza C provides a new treatment option that is superior to supportive care for patients with the MDS subtypes and specific entry criteria treated in this study.</td>
</tr>
</tbody>
</table>

| Evidence level§ | USA | 42 |

---

42 Randomised cross over trials are considered to be the same level of evidence as other RCTs. [http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/final_draft_levels_and_grades_dec_09.pdf](http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/final_draft_levels_and_grades_dec_09.pdf)
Table 11: Silverman et al. (2002) *(continued)*

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study Study size</th>
<th>Population</th>
<th>Azacitidine dose/schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crossover patients AZA n=49 Complete response=10% Partial response=4% Haematological improvement=33% Response rate=47%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 12: Kornblith et al. (2002)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study Study size</th>
<th>Population</th>
<th>Azacitidine dose/ schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kornblith (2002) USA</td>
<td>As above</td>
<td>As above</td>
<td>Quality of life was assessed by centrally conducted telephone interviews at baseline and days 50, 106, and 182. Overall quality of life, psychological state, and social functioning were assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 and the Mental Health Inventory (MHI).</td>
<td>Patients on the AZA arm experienced significantly greater improvement in fatigue (EORTC, ( p = 0.001 )), dyspnea (EORTC, ( p = 0.0014 )), physical functioning (EORTC, ( p = 0.0002 )), positive affect (MHI, ( p = 0.0077 )), and psychological distress (MHI, ( p = 0.015 )) over the course of the study period than those in the supportive care arm. Note: particularly striking were improvements in fatigue and psychological state (MHI) in patients treated with AZA compared with those receiving supportive care for patients who remained on study through at least day 106, corresponding to four cycles of AZA. Significant differences between the two groups in quality of life were maintained even after controlling for the number of RBC transfusions.</td>
<td>As above</td>
<td>Improved quality of life for patients treated with AZA coupled with significantly greater treatment response and delayed time to transformation to acute myeloid leukemia or death compared with patients on supportive care (( p &lt; 0.001 )) establishes AZA as an important treatment option for myelodysplastic syndrome.</td>
</tr>
</tbody>
</table>
**Table 13: Raza et al. (2008)**

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Azacitidine dose/schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raza (2008)</td>
<td>Phase I/II</td>
<td>Male=24</td>
<td>Azacitidine (AZA) 75mg/m²/d subcutaneous x5days every 28 days + Thalidomide 50-100 mg per day</td>
<td>MDS</td>
<td>Adverse events were generally mild (grade 1 and 2)</td>
<td>The current findings indicated that a combination of low-dose AZA and thalidomide was well tolerated and was effective therapy for the treatment of patients with MDS and AML arising from prior MDS.</td>
</tr>
<tr>
<td>Evidence level § IV USA</td>
<td>Dose escalation Novel drug combination</td>
<td>Female=12</td>
<td>IPSS LOW=2 IPSS INT-1=9 IPSS INT-2=9 IPSS HIGH=3 Unclassified=1</td>
<td>Not evaluable=0 Complete response=2 Partial response=0 Haematological improvement=11 Progressive disease=0</td>
<td>MDS and AML were not separated in the reporting of serious adverse events. Serious adverse events probably related to therapy Fever=2 events Neutropenia=3 events Abdominal pain=1 event Neuropathy=3 events</td>
<td></td>
</tr>
<tr>
<td>n=40</td>
<td></td>
<td>Male=24</td>
<td>Med (range yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluated=36</td>
<td></td>
<td>Female=12</td>
<td>IPSS INT-1=9 IPSS INT-2=9 IPSS HIGH=3 Unclassified=1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4 patients removed from study)</td>
<td></td>
<td>Median age= yrs</td>
<td>Azacitidine (AZA) 75mg/m²/d subcutaneous x5days every 28 days + Thalidomide 50-100 mg per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS=24</td>
<td></td>
<td>n=40</td>
<td>Male=24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML=12</td>
<td></td>
<td>Female=12</td>
<td>Female=24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 14: Fenaux et al. (2009)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Azacitidine dose/schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenaux (2009) Evidence level § II France/multinational</td>
<td>Phase III International (15) Multicentre (79) Controlled Parallel-group Open label Randomised trial</td>
<td>Male=151 Female=107 Median age=69yrs (range 38-88yrs) IPSS INT-1=18 IPSS INT-2=146 IPSS HIGH=167 Other=?27</td>
<td>Azacitidine arm (n=179) 75mg/m²/day for 7 d every 28 d s.c. for at least 6 cycles Total dose=525mg/m² Conventional care arm (n=179) (as selected by the investigator before randomisation) of Best supportive care n=105 (including blood product transfusions and antibiotics with granulocyte colony-stimulating factor for neutropenic infection or Low-dose cytarabine n=49 (20mg/m² / d s.c. x14d every 28 days) for at least 6 cycles or Intensive chemotherapy n=29</td>
<td>Median FU=21.1 months (IQR 15.1-26.9) until death Hazard ratio=0.58[0.43-0.77] Azacitidine arm (n=179) Median no cycles=9 (IQR 4-15) Response rate=AZA 51(29%), vs. CC21(12%) p&lt;0.0001 Median (haematological) response duration=AZA 13.6 vs.CC 5.2 months p=0.0002. Median survival = AZA 24.5 months (9.9-nor reached) vs. CC 15 months (5.6-24.1) p=0.0001. Median time to AML=AZA 17.8 months vs. CC 11.5 months p=0.0001. Not evaluable=727</td>
<td>Grade 3-4 toxicity Neutropenia AZA 91% vs CC 76% Thrombocytopenia AZA 85% vs CC 80% Anaemia AZA 57% vs CC 68% The most common treatment-related non-haematological adverse events included injection site reactions with azacitidine, and nausea, vomiting, fatigue, and diarrhoea with azacitidine, low-dose cytarabine, and intensive chemotherapy.</td>
<td>Aza C treatment results in significantly higher response rates, improved quality of life, reduced risk of leukemic transformation, and improved survival compared with supportive care. Aza C provides a new treatment option that is superior to supportive care for patients with the MDS subtypes and specific entry criteria treated in this study</td>
</tr>
</tbody>
</table>
Table 14: Fenaux et al. (2009) (continued)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Azacitidine dose/schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(induction with cytarabine 100–200 mg/m² per day by continuous intravenous infusion for 7 days, plus 3 days of either intravenous daunorubicin [45–60 mg/m² per day], idarubicin [9–12 mg/m² per day], or mitoxantrone [8–12 mg/m² per day]).</td>
<td>Haematological improvement=AZA 8749% vs. CC 51(29%) p&lt;0.0001.</td>
<td>Death 82 (AZA) vs.113 (CC)</td>
<td>Death 82 (AZA) vs.113 (CC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>all patients received best supportive care as needed</strong></td>
<td>Stable disease= AZA 75(42%) vs. CC 65(36%) p = 0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median time to progression, relapse after CR and death=AZA 14.1 months vs. CC 8.8 months p = 0.047</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 15: Lyons et al (2007)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Azacitidine dose/schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyons (2007)</td>
<td>Phase II Open label Multi centre Randomised USA n=151</td>
<td>Male= Female= Median age= yrs (range yrs) IPSS INT-1= IPSS INT-2= IPSS HIGH= RA/RARS=57% RAEB=30% Not reported=13%</td>
<td>Randomisation to one of three regimens administered every 4 weeks for 6 cycles. AZA 5-2-2 (75 mg/m² /d x5 days followed by no treatment for 2 days, followed by 75 mg/m² /d x2 days) AZA 5-2-5 (50 mg/m² /d x5 days followed by no treatment for 2 days, followed by 50 mg/m² /d x5 days) AZA 5 (75 mg/m² /d x5 days) A 12 month maintenance phase using the AZA-5 regimen every 4 or 6 weeks for patients with at least stable disease.</td>
<td>Major and minor haematological improvements were assessed using International Working Group (IWG) criteria **median no of cycle over all arms =6 Of IWG evaluable patients (n=139) 71(51%) experienced haematological improvement. AZA 5-2-2, n=50, n=46 IWG evaluable Haematological improvement=20(44%)[95% CI, 29-59] % of RBC transfusion dependent patients achieving RBC transfusion independence=55% AZA 5-2-5 n=51, n=44 IWG evaluable Haematological improvement=23(52%)[95% CI,37-68] % of RBC transfusion dependent patients achieving RBC transfusion independence=60% AZA 5 n=50, n=49 IWG evaluable</td>
<td>No treatment related mortality was reported. The profile of AEs was generally consistent over the three treatment arms. The most commonly reported AEs were administration site reactions/general disorders, haematological disorders and GI disorders. Grade 3-4 hematological adverse events AZA 5-2-2 =44% AZA 5-2-5 =33% AZA 5=18%</td>
<td>Although the efficacy and safety of the currently approved azacitidine 75 mg/m²/day s.c. for 1 week every 4 weeks regimen has been established, alternative dosing regimens that eliminate weekend dosing would be advantageous. Based on the mechanism of action of azacitidine, alternative dosing regimens should provide results consistent with those seen in previous studies.</td>
</tr>
</tbody>
</table>
Table 15: Lyons et al *(continued)*

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Azacitidine dose/schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Haematological improvement=28(57%)[95% CI, 42-71]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% of RBC transfusion dependent patients achieving RBC transfusion independence=67%</td>
</tr>
</tbody>
</table>

Hypomethylating agents in the treatment of myelodysplastic syndromes
<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Study size</th>
<th>Population</th>
<th>Azacitidine dose/schedule</th>
<th>Response N (%) [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller-Thomas et al (2009)</td>
<td>Retrospective</td>
<td>n=37 patients treated</td>
<td>Male=22, Female=10, Median age=73.1 yrs (range 60-84 yrs)</td>
<td>AZA Sub cutaneous 75mg/m²/d x7 days every 28 days Median no courses =4 12/32 patients received less than 4 cycles. 10 of these were treatment failures (progression or death) In 2 patients valproic acid and ATRA was added All patients had prophylactic antiemetics.</td>
<td>Overall response rate (CR+SD)=50% Complete CR=2 (6.3%) Marrow CR=3 (9.4%), SD=11 (34.4%) Haematological improvement=25% Failure/progressive disease=13 (40.6%) No response=3 (9.4%) Median response duration=64 weeks [95% CI, 56-77] Median survival =60 weeks [95% CI,11-108] Median time to AML=45weeks[95% CI, 22-68]</td>
<td>Grade3 or 4 toxicity Neutropenia=21.9% Thrombocytopenia=40.6% Transient erythema at injection site in all patients Infection=43.8% 19 deaths (AML=10, infection=1, pneumonia=2, bleeding =1, unknown=5)</td>
<td>Azacitidine was associated with a survival advantage in responding patients with MDS or sAML. These favourable results suggest that patients may benefit even from a limited number of courses.</td>
</tr>
<tr>
<td>Germany</td>
<td>Case series</td>
<td>n=32 patients data available (5 lost to FU)</td>
<td>(24 =MDS 8= secondary AML)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR=complete response, SD=stable disease.

Note: all trials were for adults only 18 years or older.
Hypomethylating agents in the treatment of myelodysplastic syndromes
## Appendix C: Decitabine Evidence Tables

### Table 17: Wijermans et al (1997)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Decitabine dose/schedule</th>
<th>Response [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wijermans (1997) Level of evidence § IV Netherlands</td>
<td>Phase II Single centre Open label Single arm (PCH-91-01) n=29</td>
<td>Elderly patients with high risk (progressive) MDS Male=17 Female=12 Could not have intensive chemotherapy due to age or co-morbidity RA=4 RARS=2 RAEB=11 RAEB-T=9 CMML=1 sAML=2 28 patients were blood and/or platelet transfusion dependent</td>
<td>Intravenous infusion continuous 72 hr 40 mg and 50 (first 21 patients) mg/m² per day for 3 days. No dose reduction was allowed</td>
<td>Response was evaluated by bone marrow aspirate and biopsy after every 2 courses. Maximum no of courses=8 If persistent CR therapy stopped if persistent partial response dose was escalated. Response rate=54% (n=15) Complete response=8 (28%) Partial response=5 (18%) Haematological improvement=2 (7%) Stable disease=3 (11%) Progressive disease=4 (14%) Median response duration=31+ weeks (actuarial) Median survival (from start of therapy)=46 wks Progression-free period=33 weeks (range 6-83 weeks) Not evaluable=2</td>
<td>All patients had severe pancytopenia, myelotoxicity was the major adverse effect leading to a prolonged cytopenic period and toxic death=5 (17%). For patients that showed a response Median time to platelet recovery=26 days (range 19-36) Time to ANC &gt;1.0x10⁹/l =36 days (range 19-47). Nausea WHO grade 2=3. No renal or pulmonary toxicity was observed.</td>
<td>Decitabine is an effective drug in the treatment of MDS patients and it probably works via its cytotoxic activity. The response rate and observed survival time is comparable with other studies.. Because of the short treatment time and limited adverse events this therapy may be superior to low dose Ara-C and of benefit to elderly MDS patients. Particularly if efficacy of DAC can maintained with the lower doses.</td>
</tr>
</tbody>
</table>
Table 18: Wijermans et al (2000)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Decitabine dose/schedule</th>
<th>Response [95% CI]</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wijermans (2000)</strong></td>
<td>Phase II</td>
<td>Male=46 Female=20</td>
<td>45 mg/m²/d for 3 days every 6 weeks to a maximum of 6 cycles</td>
<td>Overall response rate=49%[38-63]</td>
<td>Deaths during or shortly after treatment =5 Tox deaths=3</td>
<td>We were able to confirm our previous observation that decitabine therapy was effective in half of the study patients with high-risk MDS and especially active in patients with the worse prognosis.</td>
</tr>
<tr>
<td>Evidence level § IV</td>
<td>Multicentre</td>
<td>Median age=68 yrs (range 38-84yrs)</td>
<td></td>
<td>Complete response=13(20%)</td>
<td>Fever =18(27%) Infection=13(20%) Neutropenia=8(12%) Sepsis=7(11%)</td>
<td>The effect on overall survival and quality of life remains to be demonstrated in a phase III RCT.</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Open label</td>
<td>IPSS INT-1=16 IPSS INT-2=25 IPSS HIGH=25</td>
<td></td>
<td>Partial response=3(4%)</td>
<td>Neutropenia=8(12%) Sepsis=7(11%)</td>
<td></td>
</tr>
<tr>
<td>(PCH-95-11)</td>
<td>Single arm</td>
<td>No prior chemotherapy</td>
<td></td>
<td>Haematological improvement=16(24%)</td>
<td>Anemia=7(11%)</td>
<td></td>
</tr>
<tr>
<td>n=66</td>
<td></td>
<td></td>
<td></td>
<td>Stable disease=12(18%)</td>
<td>Myelosupression was the only major adverse effect observed.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Progressive disease=16(24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median response duration=31wks[22.6-37.4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median survival (from start of treatment)=15 months[13.3-16.7], n=66</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median progression free survival =25wks[4-84]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not evaluable=0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sub-groups</strong></td>
<td></td>
<td></td>
<td></td>
<td>IPSS high risk group median survival=14 months, median progression-free survival=25 weeks.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 19: Wijermans et al (2005)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Study size</th>
<th>Population</th>
<th>Decitabine dose/schedule</th>
<th>Response [95% CI]†</th>
<th>Toxicity</th>
<th>Author's Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wijermans (2005) Evidence level § IV Netherlands</td>
<td>Review of data of 3 European and 1 USA Phase II studies (PCH-91-01) (PCH-95-11) (PCH-95-06) (PCH 97-19)</td>
<td>n=177 Analyses =ITT containing 12 patients who were not evaluable</td>
<td>Elderly patients with high risk MDS Male=124 Female=53 Median age=70yrs (range38-89) IPSS INT-1=49 IPSS INT-2=55 IPSS HIGH=73 RA/RARS=23 RAEB=66 RAEB-T=65 CMML=23</td>
<td>Intravenous infusion continuous 72 hr 50 mg/m² per day for 3 days(increasing to 75mg/m² if no response) or a fixed dose of 15mg/m² per d given as 3 or 4 hour infusions for 3 consecutive days every 6 weeks</td>
<td>Response rate=49% (86/177) Complete response=43(24%) Partial response=18(10%) Haematological improvement=25(14%) Stable disease=36(20%) Progressive disease=32(18%) Median response duration=36wks [32-42] Median survival (T)=15months [12.5-17.5] Median progression free survival =NR Not evaluable=11(7%)</td>
<td>Toxic death=12(7%) from infection(8), bleeding or pancytopenia and was higher in earlier studies. At least 3 patients died from causes that were not disease related. Fever and sepsis=15(20%)</td>
<td>Whether azanucleosides are a real alternative for the treatment of elderly MDS patients needs to be further evaluated in Phase III studies. Other unanswered questions include the use of alternative treatment schedules.</td>
</tr>
</tbody>
</table>

---

Hypomethylating agents in the treatment of myelodysplastic syndromes
**Table 20: Kantarjian et al. (2006)**

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Decitabine dose/schedule</th>
<th>Response [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantarjian (2006) Evidence level § II USA</td>
<td>Phase III Randomised trial</td>
<td>Adults ≥18yrs confirmed MDS de novo or secondary Recruited 2001-2004 Median age=70yrs (range 30-85yrs) Secondary MDS=14% Decitabine IPSS INT-1=28 IPSS INT-2=38 IPSS HIGH=23 (comparator groups different)</td>
<td>15 mg/m² i.v. Over 3 hours every 8 hours for 3 days and repeated every 6 weeks (135 mg/m² per course)</td>
<td>Study endpoints= overall response rate (ORR) and time to AML transformation. Response assessed according to the IWG. Comparative analysis (Decitabine + supportive care vs. Supportive care) ORR p&lt;0.001 Overall improvement (CR+PR+HI) p&lt;0.001</td>
<td>Decitabine was well tolerated, with a manageable toxicity profile. On-study death=14% decitabine arm, 22% supportive care arm. SAEs: decitabine=69%, supportive care=56%. The most common hematologic adverse events were • neutropenia, thrombocytopenia, • anemia, • febrile neutropenia, leukopenia</td>
<td>Decitabine was found to be clinically effective in the treatment of patients with MDS, provided durable responses, and improved time to AML transformation or death. The duration of decitabine therapy may improve these results further.</td>
</tr>
</tbody>
</table>
### Table 21: Kantarjian et al. (2007)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Decitabine dose/schedule</th>
<th>Response [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantarjian et al. (2007)&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Phase II Open Label, Dose Comparison (3 arms) Parallel Assignment Randomised in an adaptive design n=95 (18 with CMML)</td>
<td>Adults with advanced MDS or CMML Male=66 Female=29 Median age=65 yrs Risk (all patients) IPSS INT-1=19 IPSS INT-2=26 IPSS HIGH= 11 NA=39</td>
<td>Intravenous over 1 hour: 20 mg/m² 5 days (n=64) or 20 mg/m² x 5 days (2 SC doses daily) (n=14) or Intravenous 10 mg/m² X 10 days (n=17) Total dose per course=100mg/m²</td>
<td><strong>All patients</strong> Objective response rate=73% (CR+PR+HR) Complete response=32(34%) Partial response=1(1%) Haematological improvement=13(13%)</td>
<td>The incidence of myelosupression associated complications was worse in the 10-day schedule. Grade 3-4 fever n=23patients/622 courses Minor infections n=24patients/622 courses Pneumonias n=20 patients/622 courses 63 (66%) of patients required hospitalisation due to decitabine therapy. No treatment related mortality.</td>
<td>Decitabine provides significant anti-MDS and anti-CMML activities with a safe toxicity profile. Increasing the dose intensity to 20mg/m² i.v. over 1 hr daily for 5 days resulted in improved epigenetic reactivation and produced the best CR rate.</td>
</tr>
</tbody>
</table>

<sup>43</sup> Pre-published online 2006
Table 22: Ruter et al (2007)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Population</th>
<th>Decitabine dose/schedule</th>
<th>Response [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruter (2007)</td>
<td>Retrospective study of responding Phase II trial patients treated for disease recurrence.</td>
<td>Elderly patients with MDS treated between 1997-2002 with low dose decitabine in 3 phase II trials who responded to treatment and were retreated at recurrence. Median age:71yrs (51-81) Male=15 Female=7 Initial treatment CR1=12 PR1=6 HI1=4 Risk IPSS INT-1=5 IPSS INT-2=4 IPSS HIGH= 13 RA=3 RAEB=10 RAEB-1= CMMoL=1 Saml=0</td>
<td>Retreatment with 15mg/m² per d given as 4 hour infusion for 3 consecutive days every 6 weeks. Patients received a median of 3 courses (range 1-6). Total dose=135mg/m²</td>
<td>Response rate=45% Complete response=1 (4%) Partial response=2 (9%) Haematological improvement=7(32%) Stable disease=3(14%) Progressive disease=9(41%) AML transformation =13(59%) Median survival (from initial Rx)=27.5 months(range 15-50+) *12 patients did not benefit from retreatment</td>
<td>3 patients died of sequelae of aggravation of cytopenia</td>
<td>Retreatment with decitabine was found to result in object responses in 45% of previous treated decitabine patients. However, the quality and duration of the second disease remissions were found to be inferior. Therefore decitabine responsive patients might derive more clinical benefit from continuation of the initial treatment.</td>
</tr>
</tbody>
</table>
### Table 23: Wijermans, Ruter et al (2008)

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study Study size</th>
<th>Population</th>
<th>Decitabine dose/ schedule</th>
<th>Response [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wijermans, Ruter (2008) Evidence level § IV Netherlands</td>
<td>Retrospective review of CMML patients recruited to 3 phase II (PCH-91-01, PCH-95-11, PCH 97-19) and 1 randomised phase III study (D-0007) n=31</td>
<td>CMML patients (WHO criteria) Male=23 Female=8 Median age=71yrs (range 53-81yrs)</td>
<td>15mg/m² per d given as 3 or 4 hour infusions for 3 consecutive days every 6 weeks. Total dose=135mg/m²</td>
<td>Response criteria were defined by an International Working Group. Overall response rate (CR+PR)=26% Complete response=3(10%) Partial response=5(16%) Haematological improvement=6(19%) Response duration(phase II pts)=38wks[19-57] Median survival (from start of treatment)=15 months Stable disease=10(32%) Progressive disease/not evaluable=6(19%)</td>
<td>Adverse events Myelosuppression and related infectious complications. Nausea and vomiting (42%) Pneumonia (21%) Epistaxis (11%) Diarrhea (11%) Persistent thrombocytopenia (11%). Toxic death =1(3%)</td>
<td>Our retrospective review demonstrates encouraging activity for decitabine in CMML with the possibility of cytogenetic remissions.</td>
</tr>
</tbody>
</table>

Hypomethylating agents in the treatment of myelodysplastic syndromes
<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of study</th>
<th>Study size</th>
<th>Population</th>
<th>Decitabine dose/schedule</th>
<th>Response [95% CI]†</th>
<th>Toxicity</th>
<th>Author’s Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wijermans, Suciu (2008)</td>
<td>EORTC Phase III Randomised Open-label</td>
<td>Multicentre (n=40)</td>
<td>Median age=70yrs (range 60-90yrs) Male=149 Female=84 IPSS INT-1=NR IPSS INT-2=55% IPSS HIGH= 38% Poor risk cytogenetics=46% Primary or secondary MDS or CMML 20% of patients had prior Rx for MDS</td>
<td>Arm I Decitabine 15 mg/m² i.v. over 4 hours every 8 hours for 3 days every 6 weeks for 4-8 courses in the absence of disease progression or unacceptable toxicity. Arm II: Patients received standard supportive care. Quality of life is assessed at baseline, every 6 weeks during therapy, every 2 months for 1 year, and then every 3 months thereafter. <strong>40% received a maximum of 2 cycles</strong></td>
<td>Decitabine vs supportive care Response rate=Median survival = Complete response=13% vs.0% Partial response=6% vs. 0% Haematological improvement=15% vs.2% Median response duration=0.72yrs Stable disease=14% vs. 22% Progressive disease=29% vs. 68% Not evaluable=8% vs. 8%</td>
<td>Cytopenia related toxicity arising from disease or hematotoxicity. Decitabine vs supportive care CTC grade 3-4 febrile neutropenia 26% vs. 7% CTC grade 3-4 infection 59% vs. 47% Non-Haematological: GI grade 1-2 nausea 28% vs. 16% GI grade 1-2 vomiting 16% vs. 9% Deaths: Decitabine =29 Supportive care=25 Progression to AML 7 vs. 20 Toxicity 9 vs. 0 Progression and/or toxicity 10 vs. 1 Other 3 vs. 4</td>
<td>Decitabine was found to be an effective drug in these high risk MDS patients with an over response rate of 34% leading to a significant PFS in the treatment arm. Time to AML or death was not significantly different. Due to shorter treatment duration and perhaps to treatment administered after disease progression survival, differences were not significant.</td>
</tr>
</tbody>
</table>

§ See Appendix J  
† Where reported. ‡ reported for decitabine only. * only current publication for the final results of this RCT identified.  
s.c.=subcutaneous, i.v.=intravenous,
Appendix D: Hazard Ratios for Sub-populations

![Diagram showing hazard ratios and 95% confidence intervals for overall survival in the intention to treat analysis.](source)

Source: (Fenaux, et al., 2009)

**Figure 8:** Hazard ratios and 95% confidence intervals for overall survival in the intention to treat analysis.
### Appendix E: Recruiting Azacitidine Trials (clinical trials.govt)

<table>
<thead>
<tr>
<th>Title</th>
<th>Recruitment</th>
<th>Study Results</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Phases</th>
<th>Other IDs</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplastic Syndromes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic Syndromes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorinostat and Azacitidine in Treating Patients With Myelodysplastic</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>Leukemia</td>
<td>Myelodysplastic Syndromes</td>
<td>Drug: azacitidine</td>
<td>Phases I</td>
<td>Phase II</td>
</tr>
<tr>
<td>Syndromes or Acute Myeloid Leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azacitidine With or Without MS-275 in Treating Patients With</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>Leukemia</td>
<td>Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Acute</td>
<td>Drug: azacitidine</td>
<td>Phase II</td>
<td>CDR0000466186</td>
</tr>
<tr>
<td>Myeloid Leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Azacytidine Prior to Allogeneic Stem Cell Transplant in High Risk</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>Leukemia</td>
<td>Myelodysplastic Syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic Syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hypomethylating agents in the treatment of myelodysplastic syndromes

Conditions: Myelodysplastic Syndrome
Interventions: Drug: 5-azacytidine
Phases: Phase II
Other IDs: MCC-11328
URL: http://ClinicalTrials.gov/show/NCT00721214

Title: Azacytidine and Bortezomib in Treating Patients With Relapsed or Refractory Acute Myeloid Leukemia or Myelodysplastic Syndromes
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Leukemia|Myelodysplastic Syndromes
|Myelodysplastic/Myeloproliferative Diseases
Interventions: Drug: azacitidine|Drug: bortezomib
Phases: Phase I
Other IDs: CDR0000588051|OSU-07095|OSU IRB-2008C0004|Millennium-X05247
URL: http://ClinicalTrials.gov/show/NCT00624936

Title: Revlimid and Azacitidine for Treating Advanced Myelodysplastic Syndrome (MDS)
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Anemia, Refractory|Myelodysplastic Syndromes
Interventions: Drug: Revlimid|Drug: Azacitidine
Phases: Phase I
Other IDs: RDCRN 5405|BMF 5405|U54 RR-19397-03
URL: http://ClinicalTrials.gov/show/NCT00326846

Title: Safety and Efficacy of Azacitidine, and Thalidomide in Higher Risk MDS (Myelodysplastic Syndrome)
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Myelodysplastic Syndrome
Interventions: Drug: 5-aza-cytidine and Thalidomide
Phases: Phase II
Other IDs: TASMC-08-MM-TLV-0069-08-CTIL
URL: http://ClinicalTrials.gov/show/NCT00704704

Title: SIMIDIS: Azacitidine and Beta Erythropoietin Treatment in Patients With Myelodysplastic Syndrome
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Myelodysplastic Syndrome
Interventions: Drug: Azacitidine|Drug: Beta Erythropoietin
Phases: Phase II
Other IDs: 2007-000972-18|SIMIDIS
URL: http://ClinicalTrials.gov/show/NCT00495547
Title: Phenylbutyrate Plus Azacitidine in Treating Patients With Acute Myeloid Leukemia, Myelodysplasia, Non-Hodgkin's Lymphoma, Multiple Myeloma, Non-Small Cell Lung Cancer, or Prostate Cancer
Recruitment: Completed
Study Results: No Results Available
Conditions: Leukemia|Lung Cancer|Lymphoma|Multiple Myeloma and Plasma Cell Neoplasm|Myelodysplastic Syndromes|Prostate Cancer
Interventions: Drug: azacitidine|Drug: sodium phenylbutyrate
Phases: Phase II
Other IDs: CDR0000068030|MSKCC-99060|NCI-T99-0091
URL: http://ClinicalTrials.gov/show/NCT00006019

Title: Safety Study of 5-Azacitidine and Standard Donor Lymphocyte Infusion (DLI) to Treat Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) Relapsing After Allogeneic Stem Cell Transplantation
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Myelodysplastic Syndrome|Acute Myeloid Leukemia
Interventions: Drug: 5-Azacitidine
Phases: Phase II
Other IDs: AZARELA_HHU_2007
URL: http://ClinicalTrials.gov/show/NCT00795548

Title: Phase I/II Study of 5-Azacytidine With Ara-C in Patients With Relapsed/Refractory AML or High Risk MDS
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Acute Myelogenous Leukemia|Myelodysplastic Syndrome|Leukemia
Phases: Phase I|Phase II
Other IDs: 2005-0291
URL: http://ClinicalTrials.gov/show/NCT00569010

Title: Safety & Pharmacokinetics Study Of Azacitidine (SC And Oral) In Subjects With MDS, AML, Lymphoma And Multiple Myeloma
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Acute Myeloid|Leukemia|Myelodysplastic Syndromes|Lymphoma|Multiple Myeloma
Interventions: Drug: azacitidine
Phases: Phase I
Other IDs: AZA PH US 2008 CL 008
URL: http://ClinicalTrials.gov/show/NCT00761722

Title: PXD101 and Azacitidine in Treating Patients With Advanced Hematologic Cancers or Other Diseases
Recruitment: Recruiting
Study Results: No Results Available
Hypomethylating agents in the treatment of myelodysplastic syndromes

Conditions: Chronic Myeloproliferative Disorder, Leukemia, Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Diseases
Interventions: Drug: azacitidine, Drug: belinostat
Phases: Phase I
Other IDs: CDR0000486418, UCCRC-14510A, NCI-7285
URL: http://ClinicalTrials.gov/show/NCT00351975

Title: A Phase II Study of Maintenance With Azacitidine in MDS Patients
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Leukemia, Myelocytic, Acute, Myelodysplastic Syndromes
Interventions: Drug: Azacitidine
Phases: Phase II
Other IDs: GFM aza05
URL: http://ClinicalTrials.gov/show/NCT00446303

Title: AVIDA The Vidaza® (Azacitidine) Patient Registry
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Myelodysplastic Syndromes
Interventions: Drug: Azacitidine
Phases: Phase II
Other IDs: AVIDA
URL: http://ClinicalTrials.gov/show/NCT00481273

Title: 5-Azacytidine Valproic Acid and ATRA in AML and High Risk MDS
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Acute Myelogenous Leukaemia (AML), Myelodysplastic Syndrome (MDS)
Interventions: Drug: 5 azacytidine - Valproic acid- Retinoic acid
Phases: Phase II
Other IDs: P050202
URL: http://ClinicalTrials.gov/show/NCT00339196

Title: Pre-Transplant 5-Azacitidine In Patients With High-Risk Myelodysplastic Syndrome (MDS) Who Are Candidates For Allogeneic Hematopoietic Cell Transplant
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Leukemia
Interventions: Drug: 5-azacitidine, Procedure: Allogeneic Hematopoietic cell transplantation
Phases: Phase II
Other IDs: MCC-15158, USF IRB-106349
URL: http://ClinicalTrials.gov/show/NCT00660400

Title: Randomised Allogeneic Azacitidine Study
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Leukemia|AML|MDS
Interventions: Drug: Azacitidine
Phases: Phase III
Other IDs: 2008-0503
URL: http://ClinicalTrials.gov/show/NCT00887068
Title: Combination Chemotherapy With or Without Gemtuzumab Ozogamicin or Tipifarnib in Treating Patients With Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndromes
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Leukemia|Myelodysplastic Syndromes
Phases: Phase II|Phase III
Other IDs: CDR0000526121|UHW-AML16|EU-20677|ISRCTN11036523|EUDRACT-2005-002846-14|MREC-CU106
URL: http://ClinicalTrials.gov/show/NCT00454480
Title: Treatment of Imminent Haematological Relapse in Patients With AML and MDS Following Allogeneic Stem Cell Transplantation With 5-Azacitidine (Vidaza®)
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Myeloid Leukemia|Myelodysplastic Syndrome
Interventions: Drug: 5-Azacytidin
Phases: Phase III
Other IDs: TUD-RELAZA-008|2006-001040-31 (EudraCT Nr.)
URL: http://ClinicalTrials.gov/show/NCT00422890
Hypomethylating agents in the treatment of myelodysplastic syndromes
Appendix F: New and Recruiting Decitabine Trials (clinical trials.govt)

**Recruiting** Cephalon Decitabine, Arsenic Trioxide and Ascorbic Acid for Myelodysplastic Syndrome
- Condition: Myelodysplastic Syndrome
- Intervention: Drug: Decitabine, Arsenic Trioxide and Ascorbic Acid
- Phase: Phase II
- Funded By: OTHER / INDUSTRY
- Other IDs: 00011792, 7667A

**Recruiting** Decitabine and Gemtuzumab Ozogamicin in Acute Myelogenous Leukemia (AML) and High-Risk Myelodysplastic Syndrome (H-R MDS)
- Conditions: Acute Myelogenous Leukemia; Myelodysplastic Syndrome
- Interventions: Drug: Decitabine; Drug: Gemtuzumab ozogamicin
- Phase: Phase II
- Funded By: OTHER / INDUSTRY
- Other IDs: 2008-0288

**Recruiting** A Clinical Pharmacology and Exploratory Study of Decitabine Injection in Myelodysplastic Syndrome.
- Condition: Myelodysplastic Syndrome
- Intervention: Drug: Decitabine
- Phases: Phase I / Phase II
- Funded By: INDUSTRY
- Other IDs: CR015406

**Recruiting** Decitabine (DAC) w/ or w/o Valproic Acid (VPA) in Myelodysplastic Syndrome (MDS) and Acute Myelogenous Leukemia (AML)
- Conditions: Myelodysplastic Syndrome; Acute Myelogenous Leukemia
- Interventions: Drug: Decitabine; Drug: Valproic Acid
- Phase: Phase II
- Funded By: OTHER / INDUSTRY
- Other IDs: 2006-0686

**Recruiting** A Study of Decitabine Given Subcutaneously to Adults With Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS)
- Condition: Myelodysplastic Syndrome
- Intervention: Drug: Decitabine
- Phase: Phase II
- Funded By: INDUSTRY
- Other IDs: DACO-026

Hypomethylating agents in the treatment of myelodysplastic syndromes
Hypomethylating agents in the treatment of myelodysplastic syndromes

Recruiting

Decitabine and Tretinoin in Treating Patients With Myelodysplastic Syndromes
Condition: Myelodysplastic Syndromes
Interventions: Drug: decitabine; Drug: tretinoin;
Genetic: DNA methylation analysis;
Genetic: cytogenetic analysis;
Genetic: microarray analysis;
Genetic: polymerase chain reaction;
Other: flow cytometry;
Other: immunohistochemistry staining method
Phases: Phase I / Phase II
Funded By: OTHER / NIH
Other IDs: CDR0000499783, MSKCC-06054

Recruiting

Lenalidomide and Decitabine in High Grade Myelodysplastic Syndromes
Condition: Myelodysplastic Syndromes
Intervention: Drug: Lenalidomide, Decitabine
Phase: Phase I
Funded By: OTHER / INDUSTRY
Other IDs: 00010179

Recruiting

Decitabine, Arsenic Trioxide and Vitamin C for Myelodysplastic Syndromes
Condition: Myelodysplastic Syndromes
Interventions: Drug: Decitabine; Drug: Ascorbic Acid;
Drug: Arsenic Trioxide
Phase: Phase I
Funded By: OTHER / INDUSTRY
Other IDs: 07-0916

Recruiting

A Study of Decitabine, Low Dose Cytarabine and Granulocyte Colony-Stimulating Factor (G-CSF) in High-Risk Myelodysplastic Syndromes, Refractory Acute Myeloid Leukemia or Acute Myeloid Leukemia in Patients With Significant Co-Morbidities
Conditions: Myelodysplasia; Leukemia
Intervention: Drug: decitabine, G-CSF, ARA-c
Phase: Phase II
Funded By: OTHER
Other IDs: BrUOG-AML-217, MGI Pharma#DAC 022/2007

Recruiting

LBH589 Plus Decitabine for Myelodysplastic Syndromes or Acute Myeloid Leukemia
Conditions: Leukemia, Myeloid, Acute;
Myelodysplastic Syndromes
Interventions: Drug: LBH589; Drug: Decitabine
Phases: Phase I / Phase II
Funded By: OTHER
Other IDs: 08-0172
<table>
<thead>
<tr>
<th>Recruiting</th>
<th>Clofarabine Plus Low-Dose Cytarabine Induction and Decitabine Consolidation in Frontline AML and High-Risk MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions:</td>
<td>Acute Myeloid Leukemia; Myelodysplastic Syndrome</td>
</tr>
<tr>
<td>Interventions:</td>
<td>Drug: Clofarabine; Drug: Cytarabine; Drug: Decitabine</td>
</tr>
<tr>
<td>Phase:</td>
<td>Phase II</td>
</tr>
<tr>
<td>Funded By:</td>
<td>OTHER / INDUSTRY</td>
</tr>
<tr>
<td>Other IDs:</td>
<td>2007-0039</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recruiting</th>
<th>Efficacy and Safety of ON 01910.Na in Myelodysplastic Syndrome (MDS) Patients With Trisomy 8 or Classified as Intermediate-2 or High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition:</td>
<td>Myelodysplastic Syndrome</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Drug: ON 01910.Na</td>
</tr>
<tr>
<td>Phase:</td>
<td>Phase II</td>
</tr>
<tr>
<td>Funded By:</td>
<td>INDUSTRY</td>
</tr>
<tr>
<td>Other IDs:</td>
<td>Onconova 04-17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not yet recruiting</th>
<th>Eltrombopag Treatment of Thrombocytopenia in Subjects With Advanced Myelodysplastic Syndrome (MDS) or Secondary Acute Myeloid Leukemia After MDS (sAML/MDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions:</td>
<td>Advanced Myelodysplastic Syndrome; Myelodysplastic Syndrome; Secondary Acute Myeloid Leukemia After MDS; Thrombocytopenia</td>
</tr>
<tr>
<td>Interventions:</td>
<td>Drug: eltrombopag olamine; Other: Placebo</td>
</tr>
<tr>
<td>Phase:</td>
<td>Phase I</td>
</tr>
<tr>
<td>Funded By:</td>
<td>INDUSTRY</td>
</tr>
<tr>
<td>Other IDs:</td>
<td>112509</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not yet recruiting</th>
<th>Study of Decitabine Treatment for Taiwanese Myelodysplastic Syndrome Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition:</td>
<td>Myelodysplastic Syndrome</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Drug: Decitabine</td>
</tr>
<tr>
<td>Phase:</td>
<td>Phase II</td>
</tr>
<tr>
<td>Funded By:</td>
<td>INDUSTRY</td>
</tr>
<tr>
<td>Other IDs:</td>
<td>CR014785</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not yet recruiting</th>
<th>Decitabine and Clofarabine in Higher Risk Myelodysplastic Syndromes (MDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition:</td>
<td>Myelodysplastic Syndrome</td>
</tr>
<tr>
<td>Interventions:</td>
<td>Drug: Decitabine; Drug: Clofarabine</td>
</tr>
<tr>
<td>Phase:</td>
<td>Phase II</td>
</tr>
<tr>
<td>Funded By:</td>
<td>OTHER / INDUSTRY</td>
</tr>
<tr>
<td>Other IDs:</td>
<td>2008-0092</td>
</tr>
</tbody>
</table>
Hypomethylating agents in the treatment of myelodysplastic syndromes
### Appendix G: Overview of azacitidine studies

**Table 25: Overview of azacitidine studies to support efficacy in MDS patients**

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Subcutaneous</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subcutaneous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>No. of MDS patient treated with azacitidine</td>
<td>75</td>
<td>99</td>
</tr>
<tr>
<td>Patient population</td>
<td>RAEB, RAEB-T or CMMoL w/ IPSS High or INT-2</td>
<td>RA, RARS, RAEB, RAEB-T or CMMoL</td>
</tr>
<tr>
<td>Type of control</td>
<td>Controlled</td>
<td>Controlled</td>
</tr>
<tr>
<td>Comparator arm</td>
<td>CCR</td>
<td>BSC</td>
</tr>
<tr>
<td>Study sponsorship</td>
<td>Applicant</td>
<td>CALGB/NCI</td>
</tr>
<tr>
<td>Dose regimen</td>
<td>75 mg/m² s.c. x 7d q 28d</td>
<td>75 mg/m² s.c. x 7d q 28d</td>
</tr>
<tr>
<td>Primary purpose of study</td>
<td>Pivotal efficacy</td>
<td>Supportive efficacy</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Overall Survival</td>
<td>Response rate</td>
</tr>
</tbody>
</table>
Hypomethylating agents in the treatment of myelodysplastic syndromes
Appendix H: CALGB Studies

Table 26: CALGB studies - Summary of response assessment (ITT)

<table>
<thead>
<tr>
<th>Response assessment</th>
<th>Subcutaneous (CALGB 9221)</th>
<th>Intravenous (CALGB 8921)</th>
<th>Intravenous (CALGB 8421)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azacitidine n=99</td>
<td>BSC n=92</td>
<td>Azacitidine n=72</td>
</tr>
<tr>
<td>Overall (CR + PR)</td>
<td>16 (16.2)</td>
<td>0 (0.0)</td>
<td>10 (13.9)</td>
</tr>
<tr>
<td></td>
<td>9 (18.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Remission(CR)</td>
<td>6 (6.1)</td>
<td>0 (0.0)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td></td>
<td>3 (6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial Remission (PR)</td>
<td>10 (10.1)</td>
<td>0 (0.0)</td>
<td>6 (8.3)</td>
</tr>
<tr>
<td></td>
<td>6 (12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to death from any cause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In percentage</td>
<td>95 (96.0)</td>
<td>86 (93.5)</td>
<td>70 (97.2)</td>
</tr>
<tr>
<td>Median (months)</td>
<td>20.1</td>
<td>15.4</td>
<td>11.6</td>
</tr>
<tr>
<td>95% CI on median</td>
<td>16.9, 26.4</td>
<td>13.4, 20.1</td>
<td>8.7, 17.8</td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>0.6064</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Time to transformation to AML or death (excluding patients with AML at baseline)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In percentage</td>
<td>85 (95.5)</td>
<td>77 (92.8)</td>
<td>54 (98.2)</td>
</tr>
<tr>
<td>Median (months)</td>
<td>17.7</td>
<td>13.8</td>
<td>10.1</td>
</tr>
<tr>
<td>95% CI on median</td>
<td>14.2, 22.9</td>
<td>9.3, 16.4</td>
<td>5.9, 15.7</td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>0.4789</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Time to transformation to AML (excluding patients with AML at baseline)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In percentage</td>
<td>31 (34.8)</td>
<td>33 (39.8)</td>
<td></td>
</tr>
<tr>
<td>Median (months)</td>
<td>45.8</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>95% CI on median</td>
<td>28.3, DNE</td>
<td>16.4, DNE</td>
<td></td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>0.1555</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

* Includes all 5 MDS subtypes RA, RARS, RAEB, RAEB-T, and CMMoL
* Includes all the MDS subtypes of RAEB, RAEB-T, and CMMoL
* Includes all the MDS subtypes of RAEB and RAEB-T

BSC=best supportive care, NA=not applicable
**Appendix I: Levels of Evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention ¹</th>
<th>Diagnostic accuracy ²</th>
<th>Prognosis</th>
<th>Aetiology ³</th>
<th>Screening Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I ⁴</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
</tr>
<tr>
<td>II</td>
<td>A randomised controlled trial</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among consecutive persons with a defined clinical presentation ⁶</td>
<td>A prospective cohort study</td>
<td>A prospective cohort study</td>
<td>A randomised controlled trial</td>
</tr>
<tr>
<td>III-1</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among non-consecutive persons with a defined clinical presentation ⁶</td>
<td>All or none ⁶</td>
<td>All or none ⁶</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
</tr>
<tr>
<td>III-2</td>
<td>A comparative study with concurrent controls:  - Non-randomised, experimental trial  - Cohort study  - Case-control study  - Interrupted time series with a control group</td>
<td>A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence</td>
<td>Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial</td>
<td>A retrospective cohort study</td>
<td>A comparative study with concurrent controls:  - Non-randomised, experimental trial  - Cohort study  - Case-control study</td>
</tr>
<tr>
<td>III-3</td>
<td>A comparative study without concurrent controls:  - Historical control study  - Two or more single arm study ¹⁰  - Interrupted time series without a parallel control group</td>
<td>Diagnostic case-control study ⁶</td>
<td>A retrospective cohort study</td>
<td>A case-control study</td>
<td>A comparative study without concurrent controls:  - Historical control study  - Two or more single arm study</td>
</tr>
<tr>
<td>IV</td>
<td>Case series with either post-test or pre-test/post-test outcomes</td>
<td>Study of diagnostic yield (no reference standard) ¹¹</td>
<td>Case series, or cohort study of persons at different stages of disease</td>
<td>A cross-sectional study or case series</td>
<td>Case series</td>
</tr>
</tbody>
</table>

¹ p = Population, I = Intervention/index test/indicator, C = Comparison, O = Outcome.

**Table 27:** NHMRC Evidence hierarchy: designations of “levels of evidence” according to type of research question (including explanatory notes).
Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence (NHMRC 2000b).

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the ‘Intervention’ hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the ‘Aetiology’ hierarchy of evidence should be utilised.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al.2003).

6 Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the
absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

10 Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

**Note A:** Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

**Note B:** When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.