

**REGIONAL DRUG AND THERAPEUTICS CENTRE  
(NEWCASTLE)**

**THE USE OF AZACITIDINE  
FOR THE MANAGEMENT OF  
MYELODYSPLASTIC SYNDROMES**

**Wolfson Unit  
Claremont Place  
Newcastle upon Tyne  
NE2 4HH**

**May 2009**



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## ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

<b>Subject</b>	<b>Date issued</b>
The use of aprepitant for the prevention of chemotherapy induced nausea and vomiting	March 2009
Current therapeutic strategies for pulmonary arterial hypertension	March 2009
The use of lapatinib in the management of metastatic breast cancer	November 2008
The use of liposomal doxorubicin in the management of metastatic breast cancer	October 2008
The use of dasatinib in the management of acute lymphoblastic leukaemia in adults	August 2008
The use of bevacizumab in the management of metastatic breast cancer <b>(N)</b>	September 2007
The use of entecavir in the management of chronic hepatitis B infection <b>(N)</b>	March 2007
The use of natalizumab in the management of multiple sclerosis <b>(N)</b>	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer <b>(N)</b>	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma <b>(N)</b>	June 2006
Bortezomib second-line in the management of multiple myeloma <b>(N)</b>	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer <b>(N)</b>	March 2006
Erlotinib in the management of non-small cell lung cancer <b>(N)</b>	March 2006

*Older reports are available via our website or on request*

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by **(N)** after the report name. Please refer to the NICE website to access their guidance for these agents/conditions.

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## SUMMARY

- The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal cell disorders characterised by impaired haematopoiesis associated with cytopenias leading to transfusion-dependent anaemia, an increased risk of infection or bleeding, and an increased risk of leukaemic transformation.
- There are currently no drugs licensed specifically for the treatment of MDS. Supportive care has been the historic standard of care for the management of patients with good prognosis MDS. More aggressive therapy such as intensive chemotherapy or allogeneic stem cell transplantation is an option for a minority of patients with more severe disease.
- Azacitidine (Vidaza<sup>®</sup>, Celgene Corporation) is a nucleoside analogue of cytidine. It is licensed for the treatment of adult patients who are not eligible for haematopoietic stem-cell transplantation (SCT) with Intermediate-2 and high-risk MDS, chronic myelomonocytic leukaemia, or acute myeloid leukaemia. The recommended dose is 75 mg/m<sup>2</sup> administered by subcutaneous injection daily for seven days and repeated every 28 days.
- The efficacy of azacitidine for the treatment of adults with MDS has been evaluated in two prospective, randomised, controlled phase III trials.
- In previously untreated MDS patients, azacitidine demonstrated a clinically significant increase in median survival of 9.4 months as compared with conventional care regimens, including low-dose cytarabine and intensive chemotherapy (median survival 24.4 months vs. 15.0 months, p=0.0001).
- In comparison with best supportive care alone, the overall response rate in azacitidine treated patients was significantly higher than the response rate in the supportive care group (60% vs. 0%, respectively, p<0.0001). In the azacitidine treatment arm, 7% had a complete response, 16% had a partial response, and 37% showed improvement. In the supportive-care arm, there were no responses, and only 5% of patients exhibited improvement.
- In the phase III clinical trial the major adverse events were gastrointestinal (nausea, vomiting and diarrhoea), myelosuppression (leucopenia, thrombocytopenia and neutropenia) and injection site reactions.
- Azacitidine represents an advance in the treatment of MDS over current care regimens and it is expected to become the standard of care for the treatment of higher-risk MDS patients who are not eligible for SCT.
- Azacitidine currently costs £321.00 per 100mg vial (excluding VAT). If each patient receives an average of nine cycles of azacitidine therapy, the total cost of treatment could be around £40,446 per patient. From the trial data increase in overall survival was approximately 9.4 months, thus the cost per life year gained is approximately £51,600. Alternatively using the NNT figures, it is likely to cost £161,700 for four patients to receive azacitidine for one additional patient to survive at least two years. The cost of azacitidine treatment would initially be additional to the cost of supportive care, but savings in hospitalisations and supportive care products (red cells, platelets and antibiotics) will partially offset the drug costs in responders.

## BACKGROUND

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal cell disorders characterised by impaired haematopoiesis associated with cytopenias leading to transfusion-dependent anaemia, an increased risk of infection or bleeding, and an increased risk of leukaemic transformation.<sup>1,2</sup> The overall incidence is approximately four per 100,000 population, but rises to > 30 per 100,000 in the over-70 year age group.<sup>1</sup> MDS can affect all age groups, but occurs primarily in people over 60 years old.<sup>1</sup>

Although most patients have no obvious cause for their disease, exposure to high levels of certain chemicals (particularly benzene) and ionising radiation are thought to be potential aetiological factors.<sup>3,4</sup> Therapy-related MDS can arise in patients following chemotherapy or radiotherapy treatment for primary malignancies.<sup>3,4</sup> The pathophysiology of most subtypes of MDS is poorly understood, with some patients having more indolent disease and longer life-expectancy, and others presenting with aggressive disease that rapidly progresses to leukaemia.<sup>5</sup> Regardless of initial presentation or disease course around 30% of cases of MDS will transform to acute myelogenous leukaemia (AML).<sup>2,6</sup>

## CLASSIFICATION AND PROGNOSIS

The French-American-British (FAB) classification system was originally used to categorise patients for diagnostic evaluation of MDS.<sup>2,7</sup> Patients were classified as having one of five subtypes of disease: refractory anaemia (RA), refractory anaemia with ringed sideroblasts (RARS), refractory anaemia with excess blasts (RAEB), refractory anaemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukaemia (CMML, table 1). This system has largely been superseded by the WHO classification, which records the number of lineages in which dysplasia is seen and changes the threshold maximal blast percentage for the diagnosis of MDS from 30% to 20% (table 2).<sup>2,7</sup>

**Table 1. French-American-British (FAB) Classification of MDS (Adapted from NCCN).<sup>7</sup>**

Fab subtype	Blasts in peripheral blood (%)	Blasts in bone marrow (%)
Refractory anaemia (RA)	< 1	< 5
Refractory anaemia with ring sideroblasts (RARS)	< 1	< 5
Refractory anaemia with excess blasts (RAEB)	< 5	5 – 20
Refractory anaemia with excess blasts in transformation (RAEB-T)	≥ 5	21 – 30
Chronic myelomonocytic leukaemia (CMML)	< 5	5 – 20

**Table 2. WHO Classification of MDS (Adapted from NCCN).<sup>7</sup>**

Subtype	Blood	Bone marrow
Refractory anaemia (RA)	Anemia blasts absent or rare	Erythroid dysplasia only < 5% blasts < 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (2 or more lineages); blasts absent or rare; no Auer rods; monocytes < 1 x 10 <sup>9</sup> /L	Dysplasia in at least 10% of cells and at least 2 myeloid lineages; < 5% blasts; no Auer rods; < 15% ringed sideroblasts
Refractory anaemia with ringed sideroblasts (RARS)	Anaemia, blasts absent	Erythroblast dysplasia only; < 5% blasts; at least 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (2 or more lineages); blasts absent or rare; no Auer rods; monocytes < 1 x 10 <sup>9</sup> /L	Dysplasia in at least 10% of cells and at least 2 myeloid lineages; < 5% blasts; no Auer rods; at least 15% ring sideroblasts
Refractory anaemia with excess blasts 1 (RAEB-1)	Cytopenias; < 5% blasts; no Auer rods; monocytes < 1 x 10 <sup>9</sup> /L	Uni- or multilineage dysplasia; 5 - 9% blasts; no Auer rods
Refractory anaemia with excess blasts 2 (RAEB-2)	Cytopenias; 5% -19% blasts; Auer rods present or absent; monocytes < 1 x 10 <sup>9</sup> /L	Uni- or multilineage dysplasia; 10–19% blasts; Auer rods present or absent
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias; no or rare blasts; no Auer rods	Unilineage dysplasia (granulocyte or megakaryocyte lineage); < 5% blasts; no Auer rods
MDS associated with isolated del(5q)	Anaemia; < 5% blasts; platelets normal or increased	Normal or elevated megakaryocytes with hypolobulated nuclei; < 5% blasts, no Auer rods; 5q-deletion only

The International Prognostic Scoring System (IPSS) relies on the number of cytopenias, cytogenetic profile, and the percentage blasts in the bone marrow to group patients with MDS into one of four prognostic categories (table 3).<sup>7,8</sup> In addition to age, a

patient's IPSS risk category is essential in planning therapeutic options because it provides a risk-based patient evaluation.<sup>7</sup> One of the foremost clinical features of MDS is symptomatic anaemia, with associated fatigue, which occurs in the vast majority (60%-80%) of patients. MDS is often associated with cytopenias that may also contribute to the patients symptoms, including neutropenia and dysfunctional neutrophils leading to an increased incidence of recurrent infections. In more advanced forms of MDS thrombocytopenia may result in spontaneous bruising or bleeding.<sup>4,9</sup>

Prognosis is highly dependent on subtype classification and IPSS score. The majority of patients with higher-risk MDS eventually experience bone marrow failure. Many patients with MDS will succumb to complications, such as infection or bleeding, before progressing to AML.<sup>2</sup> Patients with MDS have a median survival of around five months to over five years depending on risk stratification (table 3). Higher-risk patients have a median survival of around five to 13 months.

**Table 3. International Prognostic Scoring System for MDS (Adapted from NCCN,<sup>7</sup> and Greenberg et al.,1997<sup>8</sup>)**

Score					
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%) <sup>†</sup>	<5	5 – 10	---	11 – 20	21 – 30
Cytogenetics*	Good	Intermediate	Poor		
Cytopenias <sup>♦</sup>	0/1	2/3			
Prognosis					
Risk category (% IPSS population)	Overall score	Median survival (years) <sup>‡</sup>	25% AML progression (years) <sup>‡</sup>		
Low (33)	0	5.7	9.4		
INT-1 (38)	0.5 – 1.0	3.5	3.3		
INT-2 (22)	1.5 – 2.0	1.1	1.1		
HIGH (7)	≥ 2.5	0.4	0.2		

<sup>†</sup>Patients with 20-30% blasts may be considered as MDS or AML.<sup>7</sup>

\*Cytogenetics: Good = normal, -Y, del(5q), del(20q); Poor= complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate= other abnormalities.

<sup>♦</sup>Cytopenias: neutrophil count <1,800/mcL, platelets <100,000/mcL. Hb <10g/dL.<sup>7</sup>

<sup>‡</sup>In the absence of therapy.

## CURRENT MANAGEMENT

The British Committee for Standards in Haematology published a consensus guideline in 2003 for the treatment of MDS.<sup>1</sup> There are currently no drugs licensed specifically

for the treatment of MDS. Supportive care has been the historic standard of care for the of management of patients with good prognosis MDS, and for those with poor prognosis disease whose age or performance status precludes them from receiving more intensive forms of therapy.<sup>1,9</sup> Supportive care in the form of blood and platelet transfusions and the administration of haematopoietic growth factors aims to control symptoms, prevent and treat complications and improve quality of life.<sup>1,9</sup> For patients with a good prognosis it may be feasible to undertake a period of observation without the need to introduce any specific therapy.<sup>1</sup> More aggressive therapy such as intensive chemotherapy or allogeneic stem cell transplantation is associated with significant treatment-related morbidity and mortality and is an option for a minority of patients with severe disease.<sup>2,9</sup>

Current UK management recommendations according to IPSS groups include:

- IPSS Low. Neither intensive chemotherapy nor stem cell transplantation are currently recommended; median survival for this group without treatment is 4.8 (> 60 years) and 11.8 years (< 60 years).<sup>1</sup>
- IPSS Intermediate-1. All patients under 65 years should be assessed for fitness/eligibility for allogeneic stem cell transplantation (SCT) as soon as possible after diagnosis. Intensive cytoreductive chemotherapy prior to SCT is not recommended for this group. Patients > 65 years or < 65 years and unsuitable for SCT should be offered supportive care and/or considered for growth factor therapy.<sup>1</sup>
- IPSS Intermediate-2/High.
  - *Chemotherapy plus SCT.* All patients < 65 years should again be considered as to fitness/eligibility for stem cell transplantation early after diagnosis.<sup>1</sup>
  - *Chemotherapy alone.* Both patients > 65 years and those < 65 years who are ineligible for stem cell transplantation should be considered for intensive chemotherapy alone.<sup>1</sup>
  - *Supportive care / investigational therapy.* If patients do not fall into any category for which chemotherapy ± SCT is recommended they should be offered supportive care or investigational therapies within clinical research protocols.<sup>1</sup>

## **AZACITIDINE**

Azacitidine (Vidaza ®, Celgene Corporation) is a nucleoside analogue of cytidine believed to exert its antineoplastic effects through hypomethylation of DNA, restoring normal function to tumour suppressor genes, and through direct cytotoxicity of abnormal haematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis.<sup>10</sup>

In December 2008, azacitidine was granted a full marketing authorisation for the treatment of MDS and AML in adult patients who are not eligible for haematopoietic stem-cell transplantation.<sup>11</sup>

The approved indication is for patients with:<sup>10</sup>

- Intermediate-2 and high-risk myelodysplastic syndromes (MDS), as classified using the International Prognostic Scoring System (IPSS)
- Chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts and without myeloproliferative disorder
- Acute myeloid leukaemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to the World Health Organization (WHO) classification

Azacitidine was launched in the UK in February 2009. The purpose of this report is to evaluate the efficacy and safety of azacitidine in the management of MDS in adult patients.

## EFFICACY

The efficacy of azacitidine in the treatment of adults with MDS has been evaluated in two fully published, prospective, randomised, controlled, phase III trials: the pivotal AZA-001 study,<sup>12</sup> and the supportive CALGB 9221 study.<sup>13</sup>

The international, multi-centre, open-label AZA-001 trial compared the efficacy of azacitidine versus conventional care regimens (CCR) in previously untreated high-risk MDS patients (FAB-defined as RAEB, RAEB-T, or CMML with an IPSS of Intermediate-2 or High).<sup>12,14</sup> The study included 358 patients who received either azacitidine (n = 179) at a dose of 75 mg/m<sup>2</sup> daily for seven days every 28 days with best supportive care (BSC, including blood product transfusions, antibiotics, and G-CSF for neutropenic infection), or one of three investigator preselected conventional care regimens (n = 179):

1. Low-dose cytarabine (LDAC, 20 mg/m<sup>2</sup> daily for 14 days every 28 days) plus BSC (n = 49).
2. Intensive induction/consolidation chemotherapy plus BSC (n = 25)
3. BSC alone (n = 105).

The trial did not allow the use of erythropoietin or darbepoetin, or cross-over between treatment groups.<sup>12</sup> The primary endpoint was overall survival (OS, defined as time from randomisation to death from any cause), assessed by comparison of the azacitidine group and combined CCR group.<sup>14</sup> Secondary endpoints included time to AML transformation, haematological response and improvement, RBC transfusion independence, number of infections requiring intravenous antimicrobials, and safety.<sup>12,14</sup> The study was designed with 90% power to detect an HR of 0.6 for overall survival, based on a two sided test at a significance level  $\alpha = 0.05$ , with at least 167 deaths over the 30 month study period. All analyses used the ITT population.<sup>12</sup>

The azacitidine and CCR groups were well matched at baseline with respect to FAB subtype and IPSS score.<sup>12</sup> The median age of patients was 69 years (range 38-88 years), and 70% were male. Patients received azacitidine treatment for a median

duration of nine cycles, LDAC for a median of 4.5 cycles, intensive chemotherapy for a median of one cycle, and BSC for a median of 6.2 months. After a median follow-up of 21.1 months (range 15.1-26.9 months), the Kaplan-Meier estimated OS was 24.5 months for azacitidine versus 15 months for the CCR group (absolute difference 9.4 months,  $p=0.0001$ ) with an HR of 0.58 (95% [CI, confidence interval] 0.43-0.77). At two years there was an estimated two-fold improvement in OS; 51% for azacitidine versus 26% for CCR ( $p<0.0001$ , NNT = 4, i.e. four patients need to be treated with azacitidine for one additional patient to survive at least two years). Median time to AML transformation was 17.8 months in the azacitidine group versus 11.5 months for the CCR group (HR 0.50 [95% CI: 0.35-0.70],  $p<0.0001$ ). Duration of haematological response (complete and partial remission and any haematological improvement) was significantly longer in the azacitidine group (median 13.6 months) versus the CCR group (5.2 months,  $p=0.0002$ ).<sup>12</sup>

In patients who were RBC transfusion dependent at baseline, significantly more achieved transfusion independence in the azacitidine group compared to the CCR group (45% vs. 11%, respectively,  $p<0.0001$ ).<sup>12</sup> Similarly, more patients who were RBC transfusion independent at baseline remained transfusion independent with azacitidine compared to CCR group (85% vs. 57%, respectively,  $p=0.0005$ ).<sup>15</sup> The rate of infection requiring intravenous antimicrobial treatment was reduced by around one third in the azacitidine group compared to CCR group (0.60 vs. 0.92 per patient year, respectively, relative risk 0.66, 95% CI: 0.49-0.87;  $p=0.003$ ).<sup>12</sup> Overall hospitalisation rates per patient year were significantly reduced in the azacitidine group compared to CCR, including those days due to transfusions or adverse events (all  $p<0.0001$ ).<sup>15</sup> On average, patients receiving azacitidine had approximately seven fewer days per patient-year in the hospital.<sup>15</sup>

Almost one third of the patients enrolled in the AZA-001 trial were classified as FAB: RAEB-T ( $\geq 20\%$  -30% blasts) and met the World Health Organisation criteria for AML.<sup>16</sup> A subgroup analysis of these patients showed an estimated median OS of 24.5 months with azacitidine compared to 16.0 months with CCR (HR of 0.47 [0.28-0.79],  $p=0.004$ ). At two years estimated OS in patients with AML was 50% compared to 16%, respectively ( $p=0.0007$ ). Patients treated with azacitidine had fewer infections requiring intravenous antibiotics and reduced rates of hospitalization and red blood cell transfusions.<sup>16</sup>

The multi-centre, open-label CALGB 9221 trial compared the efficacy and safety of azacitidine plus supportive care versus best supportive care alone in patients with any of the five FAB subtypes of MDS.<sup>13,14</sup> A total of 191 patients were stratified according to subtype and randomly assigned to receive azacitidine subcutaneously at a dose of 75 mg/m<sup>2</sup> daily for seven days every 28 days ( $n = 99$ ), or supportive care alone ( $n = 92$ ). Patients randomised to the supportive care group were allowed to cross-over to the azacitidine group after a minimum of four months if their disease worsened. Dosage adjustments were allowed based on response or adverse events. The use of growth factors was prohibited, but both arms received blood transfusions and antibiotics as required.<sup>13</sup> The primary endpoint was overall response rate (complete response plus partial response).<sup>14,17</sup> Complete response was defined as complete normalisation of blood cell counts and absence of myeloblasts for four weeks. Partial response was

defined as  $\geq 50\%$  restoration in the deficit from normal levels of baseline blood cell counts, absence of blasts in the peripheral blood, and a  $50\%$  decrease in myeloblasts from baseline for four weeks. Improvement was defined as  $\geq 50\%$  decrease in transfusion requirements.<sup>17</sup> Secondary endpoints were time-to-event analyses of treatment failure, AML transformation or death, overall survival and QoL.<sup>13,17</sup>

Subjects in the two arms were well matched at baseline with respect to FAB subtype and IPSS score. Of the 191 patients included in the study, independent adjudication found that 20 had a diagnosis of AML at baseline.<sup>13</sup> These patients were excluded from the primary efficacy analysis, but were included in the intention-to-treat (ITT) analysis of all patients randomised. Follow-up data were available for all 191 subjects. Forty nine (53%) subjects in the supportive care arm crossed over to the azacitidine treatment arm. The main results after a median of nine cycles of azacitidine treatment are presented below (table 4).<sup>13</sup>

**Table 4. Primary outcome**

Response	Azacitidine N=99	Supportive care N=92	Cross-over N=49
Complete	7* (7%)	0 (0%)	5 (10%)
Partial	16‡ (16%)	0 (0%)	2 (4%)
Overall (CR+PR)	23‡ (23%)	0 (0%)	7 (14%)
Improved	37‡ (37%)	5† (5%)	16 (33%)
Total	60‡ (60%)	5 (5%)	23 (47%)

\* $p=0.01$ ; ‡ $p<0.0001$  vs. supportive care.

† all five patients had improved counts while transforming to AML

The median time to treatment failure was 9.1 months for azacitidine versus 3.8 months for supportive care ( $p<0.0001$ ), and time to transformation to AML or death was 21 months versus 12 months, respectively ( $p=0.007$ ). Azacitidine prolonged median survival duration compared to patients undergoing supportive care (20 months vs. 14 months,  $p=0.10$ ). However, when the confounding effect of early-crossover to azacitidine was eliminated using a landmark analysis in patients surviving at six months, those patients initially randomised to azacitidine survived an additional 18 months versus 11 months for patients who never crossed-over or who crossed-over after six months ( $p=0.03$ ).<sup>13</sup>

The impact of azacitidine on the quality of life of the 191 patients with MDS treated in the CALGB 9221 trial was reported by Kornblith et al, 2002.<sup>18</sup> Overall quality of life, physiological state and social functioning were assessed using the European Organization for Research and Treatment of Cancer (EORTC) Questionnaire and the Mental Health Inventory. Patients who received azacitidine experienced significantly greater improvements in fatigue ( $p=0.001$ ), dyspnoea ( $p=0.0014$ ), physical functioning ( $p=0.0002$ ), positive affect ( $p=0.0077$ ), and psychological distress ( $p=0.015$ ) over

the course of the study period compared to those in the supportive care arm. After controlling for the higher number of RBC transfusions in the azacitidine treatment group, the statistically significant differences between treatments arms were still maintained, except for psychological distress. However, the non-blinded treatment allocation may have influenced the quality of life assessment.<sup>18</sup>

## ADVERSE EFFECTS

A full safety evaluation of azacitidine is confounded by the pathophysiology of MDS, which overlaps to a large degree with the most common toxicities of azacitidine. Adverse events considered to be possibly or probably related to the administration of azacitidine have occurred in 97% of patients.<sup>10,14</sup>

In the AZA-001 trial, the most commonly reported adverse events that occurred more frequently with azacitidine than with CCR were thrombocytopenia (69.7%), neutropenia (65.7%), anaemia (51.4%), constipation (50.3%), nausea (48.0%), injection site erythema (42.9%), and pyrexia (30.3%).<sup>14</sup> The most common grade 3-4 adverse events were blood and lymphatic disorders; neutropenia (61.1%), thrombocytopenia (58.3%), leucopenia (14.9%), anaemia (13.7%) and febrile neutropenia (12.6%).<sup>14</sup> Four deaths in the azacitidine group (two from sepsis and two from bleeding) and one in the CCR (LDAC) group (cerebral ischaemia) were considered to likely to be treatment related.<sup>12</sup>

In the CALGB 9221 trial, > 95% patients in both groups reported treatment-associated adverse events.<sup>17</sup> The most common adverse events associated with azacitidine treatment were myelosuppression (thrombocytopenia, neutropenia and anaemia), gastrointestinal events (nausea, vomiting, diarrhoea, constipation, and anorexia), and injection site reactions.<sup>10,13,17</sup> Serious adverse events occurred more frequently in azacitidine-treated patients (60%) than in observation patients (36%).<sup>17</sup> After adjustment for pre-existing, disease related myelosuppression, the most commonly occurring treatment-related grade 3-4 adverse events were granulocytopenia (58%), thrombocytopenia (52%) and leucopenia (43%).<sup>10,13</sup> Infection was thought to have been treatment-related in 20% of patients, and nausea and vomiting occurred in 4%. There was one treatment-related death.<sup>13</sup>

Treatment with azacitidine is associated with anaemia, neutropenia and thrombocytopenia; complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle.<sup>10</sup> Liver function tests and serum creatinine should be assessed prior to initiation of therapy, and prior to each treatment cycle. Azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment; caution is needed in patients with liver disease.<sup>10</sup> In addition, azacitidine and its metabolites are substantially excreted by the kidneys and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have reduced renal function, it may be useful to monitor renal function.<sup>10</sup>

## DOSAGE, ADMINISTRATION AND COST

The recommended starting dose of azacitidine for the first treatment cycle, regardless of baseline haematology values is 75 mg/m<sup>2</sup> administered by subcutaneous injection daily for seven days.<sup>10</sup> Cycles should be repeated every 28 days. It is recommended that patients be treated for a minimum of six cycles. Treatment may be continued as long as the patient continues to benefit or until disease progression. Patients should be monitored for haematological response and renal toxicities, with dosage delay or reduction as appropriate. In the AZA-001 study, patients received a median of nine cycles of azacitidine treatment (range 1 - 39).<sup>10,12</sup>

Azacitidine currently costs £321.00 per 100 mg vial (excluding VAT).<sup>19</sup> The cost per 28 day treatment cycle based on an average body surface area of 1.80 m<sup>2</sup> would therefore be £4,494 (based on two vials per day). If each patient receives an average of nine cycles of azacitidine therapy, the total cost of treatment could be around £40,446 per patient. The cost of azacitidine treatment would be additional to the cost of supportive care, and does not take into consideration any locally negotiated discount. However, some of the costs of azacitidine treatment would be offset by a reduction in hospitalisation, antibiotics and blood product usage, but this is not possible to quantify at this point. From the trial data increase in overall survival was approximately 9.4 months, thus the cost per life year gained is approximately £51,600. Alternatively using the NNT figures, it is likely to cost £161,700 for four patients to receive azacitidine for one additional patient to survive at least two years. There are no published pharmacoeconomic studies of azacitidine in MDS. Of those patients in the UK with MDS, around 90% may be considered eligible for drug therapy. Assuming Intermediate-2 and High risk patients account for around 29% of these (table 3),<sup>8</sup> this would leave around one patient per 100,000 population who may be considered eligible for azacitidine treatment in the UK.

There is the potential for significant impact on chemotherapy services due to the reconstitution procedure, short expiry (no longer than eight hours in the fridge), and the fact that it needs to be given daily for seven days every four weeks.<sup>10</sup>

## PLACE IN TREATMENT

Azacitidine represents an advance in the treatment of MDS over current care regimens, and it is expected to become the standard of care for the treatment of higher-risk MDS patients who are not eligible for SCT. Current guidelines recommend that, whenever possible, treatment decisions should be based on a patient's IPSS score. All patients regardless of IPSS score will require supportive care at some stage. Patients with higher-risk MDS (IPSS intermediate-2/High) have a poor-prognosis with a median survival of around five to 13 months and currently have limited therapeutic options. SCT and/or intensive chemotherapy, is suitable for only a small fraction of higher-risk patients. For patients ineligible for SCT or chemotherapy there is no satisfactory treatment currently available other than supportive care. Azacitidine has emerged as the probable treatment of choice for these patients as it is the first drug to demonstrate clinical benefits based on increased response rate, reduced risk of

leukaemic transformation, decreased transfusion requirements and increased QoL compared to supportive care in patients with all MDS subtypes.<sup>13</sup> Azacitidine is the only drug treatment proven to significantly extend survival for patients with Intermediate-2 and High-Risk MDS and AML. In previously untreated patients (RAEB, RAEB-T, or CMMoL ) azacitidine demonstrated a clinically significant increase in median survival of 9.4 months as compared to conventional care regimens, including low-dose cytarabine and intensive chemotherapy (median survival 24.5 months vs. 15.0 months,  $p=0.0001$ ).<sup>12,14</sup> In addition to extending overall survival, 45% of azacitidine treated patients achieved RBC transfusion independence.<sup>15</sup> Although adverse events were common, azacitidine is well tolerated, and does not appear to exacerbate pre-existing cytopenias or infection caused by the underlying disease.<sup>10,14</sup> Cost effectiveness (as discussed previously) is likely to be marginal, even accounting for some improvement in quality of life and reduction in associated costs involved, and this may limit its widespread introduction. Commissioning organisations will need to make informed judgements around prioritisation and local need.

## ARRANGEMENTS FOR PRESCRIBING

Due to the administration requirements of the drug and its specialist use, prescribing should be restricted to those who are experienced in the treatment of haematological malignancies. It is likely that treatment and monitoring will remain entirely within secondary care.

## FUTURE DEVELOPMENTS

Decitabine (Eisai Inc), an intravenous DNA methylation inhibitor is licensed in the US for treatment of patients with MDS of all FAB subtypes, including Intermediate-2, and High Risk IPSS groups.<sup>20</sup> Decitabine has orphan drug status in the EU and is currently undergoing phase III trials in the EU.<sup>21</sup> In December 2008, Eisai announced that it will initiate the first head-to-head study comparing decitabine and azacitidine in patients with intermediate-1 and 2, and high-risk MDS.<sup>21</sup> The open-label study will enrol 228 patients and compare complete response rates, including bone marrow response rates.

NICE guidance on the use of azacitidine for the treatment of MDS is expected in November 2009.<sup>22</sup>

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Reference	Design	Intervention	Patient numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse effects
Silverman et al, 2002. <sup>13,14</sup>  (CALGB 9221)	R, C, O, MC	Azacitidine sc. 75mg/m <sup>2</sup> for 7 days every 28 days plus BSC  BSC alone	n = 99  n = 92	Age > 15 years, diagnosed MDS (any subtype), life expectancy ≥2 months, NCI performance status ≤2, total bilirubin and serum creatinine ≤1.5 x ULN, AST/ALT ≤2 x ULN, cancer free ≥3 years and not received radiation chemotherapy for 6 months	Not stated  (patients with AML were excluded from the efficacy analysis, but included in the ITT analyses)	OR (CR+ PR)  Secondary endpoints included: Time-to-event analyses (treatment failure, AML transformation or death) overall survival and QoL	OR = 23% of patients receiving azacitidine vs. 0% for BCS (p<0.0001).  CR = 7% vs. 0% (p=0.01), PR =16% vs. 0% (p<0.0001), and improvement = 37% vs. 5% (p<0.0001), respectively.	The most common adverse events associated with azacitidine treatment were myelosuppression, gastrointestinal events and injection site events. After adjustment for pre-existing, disease related myelosuppression, the most commonly occurring treatment-related Grade 3-4 adverse reactions were granulocytopenia (58%) thrombocytopenia (52%) and leucopenia (43%). There was one treatment-related death.
Kornblith et al, 2002. <sup>18</sup>	As above	As above	As above	As above	As above	Overall QoL (psychological state, and social functioning assessed by EORTC Questionnaire and the MHI).	Fatigue (p =0.001), dyspnoea (p=0.0014), physical functioning (p=0.0002), positive affect (p=0.0077), and psychological distress (p=0.015)	As above