Azacitidine is a pyrimidine nucleoside analogue with multiple mechanisms involved in its antineoplastic action. There is evidence that RNA metabolism is the primary target of this antimetabolite, although its inhibition of DNA methylation has been proposed as the main effect responsible for its clinical efficacy in myelodysplastic syndromes.

In patients with myelodysplastic syndromes (MDS), azacitidine appears to restore normal growth and differentiation of bone marrow cells by causing hypomethylation of DNA and direct cytotoxicity on abnormal haematopoietic cells in the bone marrow. Hypomethylation may permit the normal functioning of genes that regulate differentiation and proliferation.

Azacitidine (Vidaza®) is licensed for the treatment of adult patients with the following conditions, who are not eligible for haematopoietic stem cell transplantation:

- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS),
- chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification.

The London Cancer New Drugs group had identified azacitidine for MDS as a priority, and this review has been produced as a result.

Background

There is currently no formal guidance on the use of azacitidine for MDS.

The National Institute for Health and Clinical Excellence (NICE) is due to publish a technology appraisal discussing the clinical and cost-effectiveness of azacitidine within its licensed indications in November 2009. However, in their appraisal consultation document, NICE has made the following preliminary recommendations:

- Azacitidine is not recommended as a treatment option for people with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia.
- People currently receiving azacitidine for myelodysplastic syndrome, chronic myelomonocytic leukaemia or acute myeloid leukaemia should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

According to the final scope for the evaluation by NICE, there were 1,993 people newly diagnosed with MDS in England in 2004, with over 90% of patients aged over 60 at the time of diagnosis. The mainstay of treatment for MDS is best supportive care (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, and low-dose standard chemotherapy for some patients. Stem cell transplant is not an option for the majority of patients since the patients’ age and/or comorbidities usually precludes this treatment option.

The majority of patients die of complications related to cytopenias without ever developing AML. The heterogeneity of conditions and range of severity within conditions means that while some patients with MDS will die within a few months, others will do well for years even if they are only observed.
Literature

A comprehensive search of the literature using MEDLINE (1950 onwards) and EMBASE (1980 onwards) was conducted (search date 21/04/2009), and the retrieved references reviewed to identify any additional articles of relevance. A number of websites were accessed for information, including NICE, SMC, AWMSG, National electronic Library for Medicines (NeLM), National Library for Health (NLH), and MICROMEDEX.

Search strategy:
- **EMBASE**: *AZACITIDINE/ and *MYELODYSPLASTIC SYNDROME/ - 81 results
- **Medline via PubMed**: Azacitidine as MeSH term AND Myelodysplastic Syndromes as MeSH – 144 results

Two phase III studies included in this evaluation.

Efficacy studies

The most recent phase III study investigating the use of azacitidine in myelodysplastic syndromes involved a total of 358 patients who were randomised to receive either conventional care (n=179) or azacitidine subcutaneously at a dose of 75mg/m² per day for 7 days every 28 days for at least 6 cycles (n=179).

The prospective, multicentre, parallel group, open-label study was designed to assess the effect of treatment on overall survival with azacitidine. The control arm included the 3 most commonly used treatments in high-risk myelodysplastic syndromes. Conventional care consisted of either best supportive care only, low dose cytarabine or intensive chemotherapy.

The primary endpoint was overall survival, as analysed by the comparison of azacitidine and combined conventional care groups. At a median follow-up of 21.1 months, the median Kaplan-Meier overall survival was 24.5 months in the azacitidine group, compared to 15 months in the conventional care group, a difference of 9.4 months (stratified log-rank p=0.0001). The HR for overall survival was 0.58 (95% CI 0.43 to 0.77). From the data provided in this report it would appear that for every four patients treated with azacitidine instead of conventional care, one additional patient will be alive at 21 month follow up.

The second phase III study, published in the *Journal of Clinical Oncology* evaluated the use of azacitidine compared to best supportive care in 191 patients with the myelodysplastic syndromes. Patients were stratified by FAB classification of disease.

The comparison between azacitidine and supportive care showed statistical significance for complete response, CR (p=0.01), CR with PR (p=0.0001) and CR with PR and improvement rate (p=0.0001). The median time to AML transformation or death in the supportive care group was 12 months (95% CI 8 to 15 months), compared to 21 months for the azacitidine group (16 to 27 months), p=0.007.

A separate analysis of this study evaluated the impact of azacitidine on the quality of life of patients with myelodysplastic syndromes. The researchers reported that patients in the azacitidine arm experienced statistically significant improvement 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 with supportive care.

Safety

According to the manufacturer of azacitidine, and as reported by the phase III trials, treatment with azacitidine is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles. Therefore full blood counts should be performed as needed to monitor response and toxicity, but at least prior to each treatment cycle.

Critical evaluation

It is unclear from the two phase III studies whether patients had previously received any other treatments.

Treatment allocation:

The most recent phase III study that was published in the *Lancet Oncology* compared azacitidine with conventional care that included either best supportive care, low dose cytarabine or intensive chemotherapy (with cytarabine plus either daunorubicin, idarubicin, or mitoxantrone). When comparing the results for azacitidine with the conventional care group overall, the results favoured azacitidine. However, subgroup analyses comparing azacitidine with intensive chemotherapy showed no statistical difference between the two groups. Although investigators pre-determined which of the three conventional care groups patients were allocated to, and then randomised patients to receive either azacitidine or conventional care, for those patients randomised to conventional care and in whom benefit was not observed, it would have been interesting to cross over to either azacitidine or intensive chemotherapy to see if these patients responded to these treatments.

The open-label design of the AZA-001 study meant that the results could be subject to bias and there was an imbalance in the numbers lost to follow-up. These factors could reduce the observed effectiveness of azacitidine although in reality, this mimics the decision making process where a treatment strategy would be based upon a number of factors including the patients’ age, disease status, and performance status.

Additionally, the results for the comparison with chemotherapy were less robust because of the small numbers included.
Classification of disease:
Researchers in the most recent phase III study published classified patients according to both FAB and IPSS classification of disease. The earlier phase III trial only used FAB classification. Currently, there appear to be no definitive guidance on which classification patients should be graded against. However, the license for Vidaza® uses the IPSS classification of disease, stating it is licensed for the treatment of adult patients with intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS) classification, who are not eligible for haematopoietic stem cell transplantation.

Patients with co-morbidities:
The majority of patients diagnosed with MDS are over 60 years of age. Patients at this stage often have other co-morbidities, and all such patients were excluded from the studies.

Health Economics
No published cost-effectiveness studies were located. NICE, in their appraisal consultation document gave ICERs for treatment with azacitidine of £51,139 per quality-adjusted life year (QALY) gained for those in the best supportive care group, £47,178 per QALY gained for those in the low-dose chemotherapy group, and £34,207 for those in the standard-dose chemotherapy group, as stated in the manufacturers submission. However, using the Weibull distribution method produced an estimate of the ICER of £66,209, £63,429 and £45,179 for the best supportive care, low-dose chemotherapy and standard-dose chemotherapy groups respectively.

Estimated cost per 100 000 population
The basic NHS price is £321 per 100mg vial (excluding VAT). It is estimated that an average patient would require approximately 2 vials per day, and thus 14 vials per cycle, which equates to a cost of £4,494 per treatment cycle. In the largest phase III trial the median number of cycles used was 9. Therefore, one patient receiving 9 cycles of treatment with azacitidine would cost £40,446.

From available demographics, it is unclear as to what percentage of myelodysplastic syndrome patients would be eligible for azacitidine. Since 30% of patients go on to develop AML, and if these patients were considered most eligible (high-risk) for receiving azacitidine, in England, approximately 600 patients may be eligible for the drug per year, based on the fact that 1,993 patients were diagnosed with the condition in 2004 this approximates to about 4 new cases per 100,000 population of whom about 1.2 patients per year might be considered eligible for azacitidine based on diagnosis. This equates to a cost of £48,535 per 100,000 population per year (excluding VAT).
Azacitidine for the treatment of myelodysplastic syndromes (MDS)

Introduction

Myelodysplastic syndromes are malignant diseases of bone-marrow stem-cells, characterised by ineffective hae-mopoiesis leading to peripheral-blood cytopenias, and in many patients, progression to acute myeloid leukaemia (1). The majority of patients however, die of complications related to cytopenias without ever developing neutropenia. The heterogeneity of conditions and range of severity within conditions means that while some patients with this diagnosis will die within a few months, others will do well for years even if they are only observed (2).

A majority of patients who develop MDS are over 60 years of age (3). Until recently, treatment of MDS has been limited to supportive and palliative care except in the case of younger patients with a good performance status who could undergo allogeneic stem cell transplantation (2).

MDS are subdivided using the International Prognostic Scoring System (IPSS), and the French-American-British (FAB) and World Health Organisation (WHO) classification systems (4). Based on the proportion of leukemic cells (or ‘blasts’), the presence of chromosome 7 abnormalities, and the presence of blood cytopenia, the IPSS classifies outcome as either low-risk, intermediate-1 risk, intermediate-II risk or high-risk. It is estimated that higher risk MDS subgroups (intermediate-II and high-risk) form approximately 22% and 7% of the MDS population, respectively (4).

The British Committee for Standards in Haematology (BCSH) had previously issued guidance on the diagnosis and management of the myelodysplastic syndromes (8). The Committee had recommended that, where possible, management decisions be based upon the patient’s IPSS score as calculated during a stable clinical state and not, for example, during a florid infective initial presentation.

Currently, the most widely used system for risk stratifying myelodysplastic syndrome patients is the International Prognostic Scoring System (IPSS) which has been accepted for use in clinical practice and in clinical trials. The IPSS incorporates 3 factors: the percentage blasts in the blood and bone marrow, the karyotype, and the number of peripheral cytopenias. Management of disease is tailored to address the risk level:

- Low-risk patients: the therapeutic goal should focus on addressing the haematological cytopenias since in these patients most complications are related to cytopenias and survival can be years.
- For higher risk patients extending survival is the main goal of therapy

Given the heterogeneity of the clinical course in MDS as well as the varied types of agents being studied in trials, an International Working Group (IWG) proposed response criteria for MDS trials to help in the evaluation of outcomes and permit comparison of data. The IWG criteria evaluate improvements in survival and progression, cytogenetic response, haematological improvement, and quality of life, with specific definitions for complete remission (CR), partial remission (PR), bone marrow CR, stable disease, failure, relapse after CR or PR, cytogenetic response, disease progression, and survival.

Azacitidine is a pyrimidine nucleoside analogue with multiple mechanisms involved in its antineoplastic action. There is evidence that RNA metabolism is the primary target of this antimetabolite, although its inhibition of DNA methylation has been proposed as the main effect responsible for its clinical efficacy in myelodysplastic syndromes.

In patients with myelodysplastic syndromes (MDS), azacitidine appears to restore normal growth and differentiation of bone marrow cells by causing hypomethylation of DNA and direct cytotoxicity on abnormal haematopoietic cells in the bone marrow. Hypomethylation may permit the normal functioning of genes that regulate differentiation and proliferation(4).

Azacitidine (Vidaza®) is licensed for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS),
- chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification.

The National Institute for Health and Clinical Excellence (NICE) is due to publish a technology appraisal discussing the clinical and cost-effectiveness of azacitidine within its licensed indications. According to the final scope for the evaluation by NICE, there were 1,993 people newly diagnosed with MDS in England in 2004, with over 90% of patients aged over 60 at the time of diagnosis. The mainstay of treatment for MDS is best supportive care (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, and low-dose standard chemotherapy for some patients. Stem cell transplant is not an option for the majority of patients since the patients’ age and/or comorbidities usually precludes this treatment option.

However, in their appraisal consultation document (ACD), NICE has made the following preliminary recommendations:

- Azacitidine is not recommended as a treatment option for people with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia.
- People currently receiving azacitidine for myelodysplastic syndrome, chronic myelomonocytic leukaemia or acute myeloid leukaemia should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

It appears that NICE, in its ACD is minded not to recommend the use of azacitidine, as with a likely incremental cost-effectiveness ratio (ICER) exceeding £66,000 per QALY gained, azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia would not be a cost-effective use of NHS resources. The Committee considered the treatment pathway in the UK for patients with myelodysplastic syndrome, chronic myelomonocytic leukaemia or acute myeloid leukaemia, and heard from clinical specialists that current treatment for this group of patients most often consists of best supportive care, with approximately only 10% patients able to tolerate chemotherapy.

The Committee discussed whether the benefit provided by azacitidine for the treatment of myelodysplastic syndromes,
chronic myelomonocytic leukaemia, or acute myeloid leukaemia fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee understood that the total number of people with IPSS intermediate-II and high-risk myelodysplastic syndromes in England and Wales was approximately 700. The Committee considered that life expectancy with best supportive care alone was likely to be approximately 11.5 months. It considered the evidence from the AZA-001 trial and noted that the median overall survival for patients treated with azacitidine in the best supportive care stratification group was 21.1 months. The Committee agreed that azacitidine provided an improvement in the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia and that it was likely that azacitidine would increase overall survival by approximately 9.6 months. However, the Committee remained concerned about the uncertainty in the manufacturer’s estimates of cost effectiveness, which gave ICERs for treatment with azacitidine of £51,139 per quality-adjusted life year (QALY) gained for those in the best supportive care group, £47,178 per QALY gained for those in the low-dose chemotherapy group, and £34,207 for those in the standard-dose chemotherapy group.

NICE concluded that the estimates of the ICER were not sufficiently robust to meet the criteria needed for a life-extending, end-of-life treatment. It further concluded that even if the problems with the manufacturer’s model were corrected so as to improve the robustness of the estimates, any potential decreases in the ICER would probably not be large enough to sufficiently offset the likely increase resulting from the specification of the appropriate parametric distribution for estimating overall survival. The Committee therefore concluded that, with a likely ICER exceeding £66,000 per QALY gained, azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia would not be a cost-effective use of NHS resources.

**Classification of disease**

MDS are subdivided using the International Prognostic Scoring System (IPSS), and the French-American-British (FAB) and World Health Organisation (WHO) classification systems. Based on the proportion of leukaemic cells (or ‘blasts’), the presence of chromosome 7 abnormalities, and the presence of blood cytopenia, the IPSS classifies outcome as either low-risk, intermediate-I risk, intermediate-II risk or high-risk. It is estimated that higher risk MDS subgroups (intermediate-II and high-risk) form approximately 22% and 7% of the MDS population, respectively. The FAB system divides MDS into five subgroups, including chronic myelomonocytic leukaemia (CMML), which is characterised by high numbers of white blood cells in the blood and bone marrow. The WHO system, which divides MDS into eight subgroups, does not class CMML as a type of MDS, but rather within a new category of myelodysplastic–myeloproliferative overlap syndromes.

**Clinical evidence**

Evidence for the use of azacitidine is limited to phase II studies and two phase III studies (described below).

The most recent study investigating the use of azacitidine in myelodysplastic syndromes involved a total of 358 patients who were randomised to receive either conventional care (n=179) or azacitidine subcutaneously at a dose of 75mg/m² per day for 7 days every 28 days for at least 6 cycles (n=179). This prospective, multicentre, randomised, parallel group, open-label phase III study was designed to assess the effect of treatment on overall survival with azacitidine. The control arm included the 3 most commonly used treatments in high-risk myelodysplastic syndromes. Conventional care consisted of either:

- Best supportive care only (including blood product transfusions and antibiotics with granulocyte colony stimulating factor for neutropenic infection infection)
- Low dose cytarabine 20mg/m² subcutaneously for 14 days every 28 days for at least 4 cycles, or
- Intensive chemotherapy (induction with cytarabine 100-200 mg/m² per day by continuous intravenous infusion for 7 days, plus either 3 days of either intravenous daunorubicin 45-60mg/m² per day, idarubicin 9-12mg/m² per day, or mitoxantrone 8-12mg/m² per day).

Before randomisation, investigators determined which of the 3 conventional care treatments (best-supportive care, low-dose cytarabine or intensive chemotherapy) was most appropriate for each patient, with clinical judgement based on age, ECOG performance status, and co-morbidities. Patients were then randomly assigned to receive either azacitidine or one of the above conventional care regimens. Patients were stratified by investigators according to FAB and IPSS classifications. All treatments were continued until study completion or discontinuation due to relapse, unacceptable toxicity, or disease progression as defined by the International Working Group (IWG 2000) criteria for myelodysplastic syndromes. All patients who achieved complete or partial remission after induction received one or two consolidation courses with reduced doses of the cytotoxic drugs used for induction, followed by best supportive care.

The primary endpoint was overall survival, as analysed by the comparison of azacitidine and combined conventional care groups. Efficacy analyses were by intention-to-treat, and the safety analysis included all patients who received at least one dose of study drug and one or more safety assessments thereafter. Secondary outcome measures were time to transformation to acute myeloid leukaemia, haematological response, and improvement as assessed with IWG 2000.

Of those randomised to receive conventional care, 105 patients received best supportive care, 49 patients received low dose cytarabine, and 25 patients received intensive chemotherapy. Corresponding numbers of patients receiving azacitidine were 117 patients, 45 and 17 patients respectively. The median age of the patients involved was 69 years (range 38 to 88 years), with 258 of the total (72%) being over the age of 65 years.

For patients who received azacitidine, the median number of cycles was 9, and 151 (86%) of the 175 patients in this group received the dose of 75mg/m² per day throughout the study, with no dose adjustments. Four patients in the azacitidine group and 14 patients in the conventional care group never received the allocated drug but were followed for overall survival and were included in the intention-to-treat analysis.
At the time of last follow-up, 82 patients in the azacitidine group and 113 patients in the conventional group had died. At a median follow-up of 21.1 months, the median Kaplan-Meier overall survival was 24.5 months in the azacitidine group, compared to 15 months in the conventional care group, a difference of 9.4 months (stratified log-rank p=0.0001). The HR for overall survival was 0.58 (95% CI 0.43 to 0.77). Based on Kaplan-Meier estimates, the researchers also reported that at 2 years, 50.8% of patients in the azacitidine group (42.1 to 58.8) were alive, compared with 26.2% of patients in the conventional care group (18.7 to 34.3), p<0.001. The results were further broken down with respect to pre-defined groups:

- Overall survival was better for azacitidine than conventional care in all the cytogenetic subgroups on the international prognosis scoring system (poor prognosis HR 0.53, 0.32 to 0.87, p=0.012; intermediate prognosis 0.44, 0.22 to 0.88, p=0.021; and good prognosis 0.59, 0.37 to 0.92, p=0.021).
- Results from the investigator pre-selected subgroup analysis of overall survival showed statistically significant differences favouring the study drug between azacitidine and best supportive care (21.1 months vs. 11.5 months, HR=0.58, p=0.0045), and azacitidine and cytarabine (24.5 months vs. 15.3 months, HR=0.36, p=0.0006). The difference in the comparison between azacitidine (n=17) and intensive chemotherapy (n=25) however, was not statistically significant (25.1 months vs. 15.7 months, HR=0.76, p=0.51).
- Median time to acute myeloid leukaemia transformation was 17.8 months (range 8.6 to 36.8 months, 95% CI 13.6 to 23.6) in the azacitidine group compared to 11.5 months in the conventional group (range 4.9 to not reached, 95% CI 8.3 to 14.5) – p<0.0001. The researchers reported that time to acute myeloid leukaemia transformation did not differ significantly between the azacitidine and the low-dose cytarabine (15.0 months vs. 14.5 months, HR=0.55, p=0.097) or the intensive chemotherapy groups (23.1 months vs. 10.7 months, HR=0.48, p=0.19).

### The following results were reported for haematological responses:

<table>
<thead>
<tr>
<th>Haematological response</th>
<th>Best supportive care</th>
<th>Low-dose cytarabine</th>
<th>Intensive chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azacitidine</td>
<td>p-value</td>
<td>Azacitidine</td>
</tr>
<tr>
<td>Any remission</td>
<td>27%</td>
<td>&lt;0.0001</td>
<td>31%</td>
</tr>
<tr>
<td>Complete remission</td>
<td>12%</td>
<td>0.0008</td>
<td>24%</td>
</tr>
<tr>
<td>Partial remission</td>
<td>15%</td>
<td>0.0058</td>
<td>7%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>44%</td>
<td>0.50</td>
<td>33%</td>
</tr>
</tbody>
</table>

### The table below describes secondary outcomes reported:

<table>
<thead>
<tr>
<th></th>
<th>Azacitidine</th>
<th>Conventional care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to disease progression, relapse after complete or partial remission and death</strong></td>
<td>14.1 months</td>
<td>8.8 months to 3.8 months to not reached</td>
</tr>
<tr>
<td><strong>Duration of haematological response (complete and partial remission and any haematological improvement)</strong></td>
<td>13.6 months</td>
<td>5.2 months to 2.9 to 12.2 months</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>46%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Death during first 3 months</strong></td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Discontinuation of treatment before study completion due to haematological adverse events</strong></td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Grade 3 or 4 neutropenia</strong></td>
<td>91%</td>
<td>76%</td>
</tr>
<tr>
<td><strong>Grade 3 or 4 thrombocytopenia</strong></td>
<td>85%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Grade 3 or 4 anaemia</strong></td>
<td>57%</td>
<td>68%</td>
</tr>
</tbody>
</table>
The rate of infections treated with intravenous antimicrobials per patient year in the azacitidine group was 0.60 (95% CI 0.49 to 0.73), compared to 0.92 (0.74 to 1.13) in the conventional care group (relative risk 0.66, 0.49 to 0.87, p=0.0032).

In summary, the primary outcome measure of overall survival at a median of 21.1 months was 24.5 months for the azacitidine group, and 15 months for the conventional group. Furthermore at the time of last follow up, 117 patients in the azacitidine group had survived, compared to 66 patients in the conventional care group (number needed to treat of 4).

Another phase III study, published in the Journal of Clinical Oncology evaluated the use of azacitidine compared to best supportive care in 191 patients with the myelodysplastic syndromes. Patients were stratified by FAB classification of disease, and randomised to receive treatment with either azacitidine subcutaneously 75mg/m² for 7 days every 28 days, or best supportive care.

In the azacitidine arm, patients were given the study drug in 7-day cycles beginning on days 1, 29, 57 and 85. If a beneficial effect was not observed by day 57 and no significant toxicity other than nausea and vomiting had occurred, the dose of the azacitidine was increased by 33%. Once a benefit was seen at a particular dose, administration at this dose was continued unless the patient experienced any adverse effects. Patients were assessed after the fourth cycle, and those who achieved complete remission (CR) continued on the drug for 3 more cycles; those with a partial response (PR) or improvement continued on the drug until either CR or relapse occurred. Patients who progressed during the induction phase and those with stable disease at day 113 were classified treatment failures and removed from treatment.

In the supportive care arm, after a minimum interval of 4 months of supportive care, patients whose disease was worsening were permitted to cross over to azacitidine treatment. Patients could exit supportive care before 4 months but only because of death, withdrawal of consent, transformation to acute leukaemia, or a platelet count persistently less than 20 X 10⁹/L after week 8. Patients transforming to acute myelogenous leukemia (AML) exited at any time, whilst those with less than or equal to 40% blasts in the marrow crossed over to azacitidine, and those with greater than 40% blasts received other treatments.

Complete response (CR) was defined as:
- Achieving normal bone marrow or bone marrow with <5% blasts, but some dyshaematopoietic features may persist
- Achievement of complete normalisation of the peripheral blood counts i.e. haemoglobin, white blood cells, and platelets, with 0% blasts and no requirement for blood transfusions
- A relapse in CR defined as presence of >5% blasts

Partial response was defined as:
- Achievement of <= 50% of initial bone marrow blasts
- Achievement of a trilineage response in peripheral blood counts, with 0% blasts and no requirement for transfusions
- A relapse in PR defined as the presence of >30% blasts

Criteria for an improvement in condition was defined as either a monolineage or bilineage response in bone marrow (>= 50% restitution of the initial deficit from normal in one or two peripheral blood cell counts).

The table below shows the analysis of response:

<table>
<thead>
<tr>
<th></th>
<th>Azacitidine (n=99)</th>
<th>Supportive care (n=92)</th>
<th>Cross-over (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>Percentage</td>
<td>No of patients</td>
</tr>
<tr>
<td>Complete remission</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Partial remission</td>
<td>16</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Improved</td>
<td>37</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>
Azacitidine for the treatment of myelodysplastic syndromes (MDS)

The comparison between azacitidine and supportive care showed statistical significance for CR (p<0.01), CR with PR (p<0.0001) and CR with PR and improvement rate (p<0.0001).

The following results were also reported:

- Median times to initial response and best response were 64 and 93 days respectively.
- The median duration of response among patients who achieved CR, PR or improvement was 15 months (95% CI 11 to 20 months).
- The median time to exit from supportive care (i.e. median time to treatment failure) was 3.8 months (95% CI 3.5 to 4.0 months, range 0.6 to > 55 months); the median time to exit from the azacitidine arm was 9.1 months (5.6 to 11 months, range 0.1 to > 44 months); p<0.0001
- The median time to AML transformation or death in the supportive care group was 12 months (95% CI 8 to 15 months), compared to 21 months for the azacitidine group (16 to 27 months), p=0.007
- For patients with high-risk FAB subtypes, the median time to AML or death in the supportive care group was 8 months (95% CI 4 to 13 months), compared with 19 months (13 to 21 months) for the azacitidine group (p=0.004)
- Transformation to AML occurred as the first event in 15% of patients receiving azacitidine, compared with 38% of patients randomised to supportive care (p=0.001)
- The median overall survival was 20 months (95% CI 16 to 26 months) for patients randomised to azacitidine, compared to 14 months for patients receiving best supportive care (12 to 14 months; 53% of whom received azacitidine after supportive care), p=0.10. To eliminate the confounding effect of the cross-over, an analysis was done which evaluated patients who had never been crossed over, patients who were crossed over before 6 months and patients who were crossed over after 6 months. The median survival for these 3 groups was 11, 14 and 18 months respectively, with the azacitidine group statistically significantly different from the supportive care group who crossed over late or never (p=0.03)
- Grade 3 or 4 leukopenia occurred in 43%, granulocytopenia occurred in 58% and thrombocytopenia occurred in 52% of patients receiving azacitidine. However, toxicity was transient and patients usually recovered in time for the next treatment cycle.

There was one treatment-related death in the azacitidine group

In summary, use of azacitidine was associated with improved median overall survival of 6 months, and the median time to AML transformation was extended by 9 months.

A separate analysis of this study evaluated the impact of azacitidine on the quality of life of patients with myelodysplastic syndromes. It was hypothesized that a response to azacitidine would result in improved quality of life attributable to better palliation, with less fatigue resulting in improved physical and social functioning and less psychological distress. Overall quality of life, psychological state and social functioning were assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 and the Mental Health Inventory (MHI).

The researchers reported that patients in the azacitidine arm experienced statistically significant improvement 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 with supportive care.

Side-effects

According to the manufacturer of azacitidine, and as reported by the phase III trials above, treatment with azacitidine is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles. Therefore full blood counts should be performed as needed to monitor response and toxicity, but at least prior to each treatment cycle. After administration of the recommended dose for the first cycle, the dose for subsequent cycles should be reduced or its administration delayed based on nadir counts and haematological response, and patients should be advised to promptly report febrile episodes. Additionally, patients and physicians should be advised to be observant for signs and symptoms of bleeding.

Cost

The basic NHS price is £321 per 100mg vial (excluding VAT). It is estimated that an average patient would require approximately 2 vials per day, and thus 14 vials per cycle, which equates to a cost of £4,494 per treatment cycle. In the largest phase III trial the median number of cycles used was 9. Therefore, one patient receiving 9 cycles of treatment with azacitidine would cost £40,446.

From available demographics, it is unclear as to what percentage of myelodysplastic syndrome patients would be eligible for azacitidine. Since 30% of patients go on to develop AML, and if these patients were considered most eligible (high-risk) for receiving azacitidine, in England, approximately 600 patients may be eligible for the drug per year, based on the fact that 1,993 patients were diagnosed with the condition in 2004. This would equate to a total cost of £24,267,600.

Based on the number of new cases diagnosed in 2004, approximately 4 new cases would be expected per 100,000 population. Assuming 30% of these would be eligible for treatment with azacitidine, 1.2 patients per year may be first eligible on diagnosis, equating to a cost of £48,535 per year.

It is important to note that the 7-day regimen will require considerable investment in terms of pharmacy preparation costs and drug administration costs, which have not currently been factored as service delivery costs.
Discussion points/Issues for consideration

Azacitidine requires aseptic preparation. A dosing regimen of 7 days will impact on pharmacy services at weekends for reconstitution of the product. There have been reports of use of a 5 + 2 day regimen, where patients get their doses from Monday to Friday, then a 2 day break over the weekend, then two further doses on Monday and Tuesday.

Although studies determining cost-effectiveness are lacking, the log-logistic model used for the cost per QALY concluded that the manufacturer’s base-case results gave incremental cost-effectiveness ratios (ICERs) for treatment with azacitidine of £51,139 per quality-adjusted life year (QALY) gained for those in the best supportive care group, £47,178 per QALY gained for those in the low-dose chemotherapy group, and £34,207 for those in the standard-dose chemotherapy group. Using the Weibull distribution method produced an estimate of the ICER of £56,209, £63,429 and £45,179 for the best supportive care, low-dose chemotherapy and standard-dose chemotherapy groups respectively. It is unclear as to which method should be used, and considering that ideally, eligible patients would be treated with high dose chemotherapy in order to undergo stem cell transplantation, then it may be useful to compare costs of azacitidine with that of high dose chemotherapy.

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Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal clinical study and therefore the safety and efficacy of azacitidine in these patients with other co-morbidities has not been established.

Given that NICE calculate that it is unlikely that the incremental cost per QALY gained over best supportive care is less than £66,000 and that they do not feel that at this level it should be approved even under revised end-of-life criteria, is it possible to give any alternative decision in the absence of a risk share programme (or similar) to reduce the overall cost to the NHS?

References:

5. MICROMEDEX azacitidine drug monograph [accessed 23 April 2009]
7. Vidaza (azacitidine) summary of product characteristics, date of revision = 17 December 2008

The document reflects the views of LCNDG and may not reflect those of the reviewers

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