

National Horizon Scanning Centre

Azacitidine (Vidaza) for myelodysplastic syndrome

September 2007



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Azacitidine (Vidaza) for myelodysplastic syndrome

Target group

- High-risk^a patients with myelodysplastic syndromes and acute myeloid leukaemia (<30% blasts): French-American-British cooperative group (FAB) classification - refractory anaemia with excess blasts in transformation (RAEB-T)^b.

Background

The myelodysplastic syndromes (MDS) are a group of disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. It is characterised by one or more peripheral blood cell cytopenia secondary to bone marrow dysfunction. Transformation to acute myeloid leukaemia (AML) occurs in about 30% of patients. Median survival of MDS is around 20 months.

Technology description

Azacitidine (Vidaza) is a DNA methyltransferase inhibitor that is thought to act by causing hypomethylation of DNA (epigenetic therapy), which may restore normal function to genes that are critical for differentiation and proliferation, and by direct cytotoxicity.

Azacitidine is administered subcutaneously at a dose of 75mg/m² for 7 days every 28 days for a minimum of 4 cycles and will be used alongside standard chemotherapy regimens and best supportive care. An oral version of azacitidine is in early clinical trials.

Innovation and/or advantages

Azacitidine is the first of a new class of epigenetic therapies, and has demonstrated a survival, morbidity and quality of life benefit in trials.

Developer

Pharmion Ltd.

Place of use

- | | | |
|---|---|--|
| <input type="checkbox"/> Home care e.g. home dialysis | <input type="checkbox"/> Community or residential care e.g. district nurses, physio | <input type="checkbox"/> Primary care e.g. used by GPs or practice nurses |
| <input type="checkbox"/> Secondary care e.g. general, non-specialist hospital | <input checked="" type="checkbox"/> Tertiary care e.g. highly specialist services or hospital | <input type="checkbox"/> Emergency care e.g. paramedic services, trauma care |
| <input type="checkbox"/> General public e.g. over the counter | <input type="checkbox"/> Other: | |

Availability, launch or marketing dates, and licensing plans:

Azacitidine is in Phase III clinical trials and is a designated orphan drug in the EU. Azacitidine for MDS (iv. and sc.) is licensed in the USA for all forms of MDS.

^a High risk is defined by the International Prognostic Scoring System (IPSS) which uses quantitative information about risk factors (proportion of blasts, cytogenetics, blood cytopenia) to predict disease progression and classifies outcome as either low-risk, intermediate-1-risk, intermediate-2-risk or high-risk.

^b FAB classification RAEB-T is equivalent to 'acute myeloid leukaemia (AML) with multilineage dysplasia following a myelodysplastic syndrome' under the World Health Organisation 1997 classification.

NHS or Government priority area:

- | | | |
|--|--|--|
| <input checked="" type="checkbox"/> Cancer | <input type="checkbox"/> Cardiovascular disease | <input type="checkbox"/> Children |
| <input type="checkbox"/> Diabetes | <input type="checkbox"/> Long term neurological conditions | <input type="checkbox"/> Mental health |
| <input type="checkbox"/> Older people | <input type="checkbox"/> Public health | <input type="checkbox"/> Renal disease |
| <input type="checkbox"/> Women's health | <input type="checkbox"/> None identified | <input type="checkbox"/> Other: |

This topic relates to the NHS Cancer Plan.

Relevant guidance

- NICE cancer service guideline. Haemato-oncology. October 2003¹.
- British Committee for Standards in Haematology. Guideline for the diagnosis and therapy of adult myelodysplastic syndromes. 2003. (expected review, August 2008)².

Clinical need and burden of disease

There were 1,993 people newly diagnosed with MDS in England in 2004, with a median age at diagnosis of about 75 years and over 90% of patients aged over 60 at the time of diagnosis³. Men are more likely than women to have MDS. The overall disease incidence is about 4 per 100,000 population. This rises to >30 per 100,000 in the over 70s². Incidence may be an underestimate as MDS often goes undiagnosed.

RAEB-T accounts for about 5-15% of cases (an estimated 100 to 300 people in England) and has a median survival of less than six months.

Existing comparators and treatments

There are no specifically licensed products for MDS. The current treatment and supportive options includes:

- Supportive care with
 - regular red cell and/or platelet transfusions
 - erythropoietin and granulocyte-colony stimulating factor
 - antibiotics to treat infections
- Low-intensity chemotherapy e.g. cytarabine
- High-intensity chemotherapy for AML transformation
- Bone marrow transplantation may be considered for younger patients

Efficacy and safety

There are numerous trials of azacitidine in MDS including:

- a company-sponsored phase II trial exploring different dosing regimens,
- a company-sponsored phase II trial of azacitidine in combination with histone deacetylase inhibitors,
- trials in combination with lenalidomide and etanercept,
- ongoing trials of azacitidine in low-risk patients, and
- numerous ongoing investigator initiated (non-company sponsored) trials.

Trial name or code	Azacitadine vs. supportive care. Phase III (CALGB 9221)	Azacitidine vs. conventional care; high risk MDS. Phase III (CL001)
Sponsor	National Cancer Institute	Pharmion
Status	Published ^{4,5} ; with extra subsequent analyses, re-analyses and combination analysis with phase II trials ⁶ .	Completed, press release ⁷
Location	USA	USA, Europe, Australia
Design	Randomised, non-blinded	Randomised, open-label, active-control

Participants in trial	n=191; MDS; stratified by FAB subtype. Randomised to: i) azacitidine sc 75mg/m ² for 7 days every 28 days (dose increased in 3 rd cycle if no response), or ii) best supportive care (PSC). Patients on BSC whose disease worsened after a minimum of 4 months crossed-over to azacitidine.	n=358; high-risk MDS - RAEB or RAEB-T or chronic myelomonocytic leukaemia (CMMOL); stratified by FAB subtype. Randomised to: i) azacitidine sc 75mg/m ² for 7 days every 28 days and BSC, or ii) conventional care regimens (CCR): - best supportive care (BSC) - low dose cytarabine and BSC, or - standard induction/remission chemotherapy and BSC
Follow-up	Until death – 54 months	Until death or conclusion of study.
Primary outcome	Bone marrow and/or peripheral blood response; treatment failure i.e. change in FAB subtype, transfusion dependency, and progressive bone marrow failure; survival, and quality of life.	Survival
Secondary outcomes		Haematological response; duration of response; time to leukaemic transformation or death; safety.
Key results	Response: azacitidine 60% vs. 5% on BSC (p<0.001). Response was independent of FAB subtype. Median time to leukaemic transformation or death: azacitidine 21 months vs. 12 months on BSC (p=0.007). For high-risk patients the median time was 19 months vs. 8 months (p=0.004). Median survival: 20 months for azacitidine vs. 14 months on BSC (p=0.1). Quality of life: significant advantages in physical functioning, symptoms and psychological state for azacitidine.	Interim results. Median survival: azacitidine 24.4 months vs. 15 months for CCR (p=0.0001). 2-year survival: azacitidine 50.8% vs. 26.2% for CCR (p<0.0001).
Expected reporting date	N/A	Full results expected at ASH conference in December 2007
Adverse effects	The most common adverse effect of azacitidine was transient myelosuppression; grade 3 or 4 leukopenia 59%, granulocytopenia 81% and thrombocytopenia 70%. There was 1 treatment-related death.	

Estimated cost and cost impact

The cost of azacitidine has yet to be determined.

Potential or intended impact – speculative

Patients

- | | | |
|---|---|---|
| <input checked="" type="checkbox"/> Reduced morbidity | <input checked="" type="checkbox"/> Reduced mortality or increased survival | <input checked="" type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker, earlier or more accurate diagnosis or identification of disease | <input type="checkbox"/> Other: | <input type="checkbox"/> Non identified |

Services

- | | | |
|---|--|---|
| <input type="checkbox"/> Increased use | <input type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input checked="" type="checkbox"/> Decreased use: may be a reduced need for supportive hospital-based care | <input type="checkbox"/> Other: | <input type="checkbox"/> Non identified |

Costs

- | | | |
|---|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative | <input type="checkbox"/> Increased costs: more patients coming for treatment | <input type="checkbox"/> Increased costs: capital investment needed |
| <input checked="" type="checkbox"/> New costs: New treatment, additional to current costs | <input checked="" type="checkbox"/> Savings: potentially fewer transfusions and other supportive options may be required | <input type="checkbox"/> Other: |

References

- ¹ National Institute for Clinical Excellence. Cancer Service Guideline. Improving outcomes in haemato-oncology cancer. October 2003.
- ² Bowen D, Culligan D, Jowitt S *et al.* British Committee for Standards in Haematology – Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. *British Journal of Haematology*, 2003; 120: 187-200.
- ³ Office for National Statistics. Cancer Statistics: registrations of cancer diagnosed in 2004, England. Series MB1 No.35.
- ⁴ Silverman LR, Demakos EP, Peterson BL *et al.* Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the cancer and leukaemia group B. *Journal of Clinical Oncology*, 2002; 20(10):2429-2440.
- ⁵ Kornblith AB, Herndon-II JE, Silverman LR *et al.* Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomised phase III trial: A cancer and leukaemia group B study. *Journal of Clinical Oncology*, 2002; 20(10):2441-2452.
- ⁶ Silverman LR, McKenzie DR, Peterson BL *et al.* Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921 and 9221 by the Cancer and Leukemia Group B. *Journal of Clinical oncology* 2006;24(24):3895-3903.
- ⁷ Pharmion Press release. Vidaza significantly extends overall survival by 74% on phase 3 trial in myelodysplastic syndrome. 7th August 2007.

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