

National Horizon Scanning Centre

Decitabine (Dacogen) for myelodysplastic syndrome

April 2008



This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

Decitabine (Dacogen) for myelodysplastic syndrome

Target group

- Myelodysplastic syndrome (MDS).

Technology description

Decitabine is an intravenous (IV) antimetabolite analogue of 2'-deoxycytidine (deoxycytidine and cytarabine), which inhibits DNA methylation, leading to re-expression of tumour suppressor genes and a resulting re-differentiation and maturation of cancer cells to normal. Decitabine has also been shown to restore sensitivity of tumours to drugs such as cisplatin, by reversing drug resistance.

Decitabine is being developed as a substitute and as an addition to other therapies for MDS. Decitabine is administered at 20mg/m² IV once daily for five days, every 4 weeks (outpatient basis) or 15mg/m² every 8 hours, for 3 days, every 6 weeks (inpatient basis).

Decitabine is in phase III clinical trials for acute myeloid leukaemia (AML).

Innovation and/or advantages

Decitabine may prolong survival and time to progression to acute myeloid leukaemia (AML).

Developer

Janssen-Cilag.

Availability, launch or marketing dates, and licensing plans:

Decitabine has orphan drug status for MDS in the EU and USA.

NHS or Government priority area:

This topic relates to the NHS Cancer Plan (2000).

Relevant guidance

- NICE cancer service guideline. Haemato-oncology. October 2003¹.
- Department of Health: Specialised Services National Definition Set: 2 specialised services for blood and marrow transplantation (all ages). 2007².
- British Committee for Standards in Haematology. Guideline for the diagnosis and therapy of adult myelodysplastic syndromes. 2003 (expected review, August 2008)³.

Clinical need and burden of disease

MDS is a rare group of blood disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. MDS mainly affects people over 50, with men more likely than women to have the disease. MDS has a median survival of 20 months and may progress to life-threatening failure of the bone marrow or develop into acute myeloid leukaemia (AML), which occurs in around 30% of patients. General symptoms associated with MDS include fatigue, dizziness, weakness, bruising and bleeding, frequent infections, and headaches⁴.

There were 1,993 people newly diagnosed with MDS in England in 2004⁵, and 919 registered deaths in England and Wales in 2005⁶. The median age at diagnosis is 75 years and over 90% of patients are aged over 60 at the time of diagnosis⁵.

Existing comparators and treatments

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

- Supportive care which may include:
 - 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 given to people with high-risk MDS.
- Allogenic bone marrow transplantation may be considered for younger patients with high-risk MDS or reduced intensity allograft for older patients (<65 years).

Efficacy and safety

Trial name	Advanced, higher-risk MDS and chronic myelomonocytic leukaemia (CMML) ⁷ .	Decitabine vs supportive care; phase III ⁸ .
Sponsor	MD Anderson Cancer Center, USA.	MD Anderson Cancer Center, USA.
Status	Published	Published
Location	USA	USA
Design	Randomised; uncontrolled.	Randomised; open-label.
Participants in trial	n=95 (77 MDS); advanced, higher-risk MDS and CMML. Randomised to decitabine - Arm 1: 20mg/m ² IV daily for 5 days Arm 2: 20mg/m ² SC daily for 5 days Arm 3: 10mg/m ² IV daily for 10 days	n=170; MDS. Randomised to decitabine (DAC) 15mg/m ² , every 8 hours for 3 days (at a dose of 135 mg/m ² per course) repeated every 6 weeks with supportive care vs best supportive care (SC) alone.
Follow-up	28 days	-
Primary outcome	Complete response (CR); partial response (PR) and haematologic improvement (HI).	Overall response rate (ORR); haematologic improvement (HI).
Secondary outcomes	Methylation and expression study.	Time to AML or death.
Key results	Overall 32 (34%) achieved CR; 1 (1%) achieved PR; 23 (24%) had marrow CR without (11%) or with other HI response (14%). Overall 69 out of 95 (73%) had objective responses. CR for arms 1, 2 and 3 were 39%, 21% and 24% (p<0.05) respectively. Arm 1 was also superior at inducing hypomethylation at day 5 and at activating P15 expression at days 12 or 28 after therapy. Median overall survival was 19 months. The estimated 18 month AML transformation rate was 27%.	Overall response rate for DAC, 17%, including 9% CR, compared to SC (0%) (p<0.001). 12 (13%) achieved haematologic improvement with DAC. Median response for DAC was 10.3 months and was associated with transfusion independence and trends toward longer median time to AML progression or death compared to SC (all patients, 12.1 months vs 7.8 months [p=0.16]). Those with IPSS intermediate-2 or high-risk disease had a median response of 12 months vs 6.8 months [p=0.03]; those with de novo disease 12.6 months vs 9.4 months [p=0.04]; and treatment-naive 12.3 months vs 7.3 months [p=0.08]).
Adverse effects	Severe (grade 3-4) toxicities uncommon; liver toxicities in 4 (4%). There were 4 deaths due to myelosuppression-associated complications	-
Trial name	NCT00043134; EORTC-06011 ⁹ : low-	NCT00260065; DACO-020 ¹⁰ :

	dose decitabine vs supportive care; phase III.	alternative dosing for out-patients, phase II.
Sponsor	European Organization for Research and Treatment of Cancer (EORTC).	MGI Pharma
Status	Ongoing	Ongoing
Location	UK, Europe.	North America.
Design	Randomised; open-label.	Non-randomised; open label.
Participants in trial	n=220; >60 years; primary MDS (>10% blasts or high-risk cytogenetics), secondary MDS or CMML; not eligible for intensive therapy. Randomised to decitabine 15mg/m ² IV, every 8 hours for 3 days, every 6 weeks for 4-8 courses with supportive care vs supportive care alone.	n=93; advanced-stage MDS. Decitabine 20mg/m ² daily for 5 consecutive days, every 4 weeks.
Follow-up	2 years	2 years
Primary outcome	Overall survival (OS)	ORR
Secondary outcomes	Response rate; progression free survival (PFS); toxicity; quality of life; days in hospital; number of transfusions.	Haematologic improvement; cytogenetic response; time to AML progression (≥30% blasts) or death; transfusion requirements; toxicity.
Expected reporting date	The study started in May 2002 and is expected to finish in May 2008.	Final analysis is underway.

Estimated cost and cost impact

Additional costs include those associated with IV infusion.

Potential or intended impact – speculative

Patients

- | | | |
|---|---|---|
| <input 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"/> None identified |

Services

- | | | |
|---|--|--|
| <input checked="" type="checkbox"/> Increased use | <input type="checkbox"/> Service reorganisation required | <input checked="" type="checkbox"/> Staff or training required |
| <input type="checkbox"/> Decreased use | <input type="checkbox"/> Other: | <input type="checkbox"/> None 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: No specific licensed therapy | <input type="checkbox"/> Savings: | <input type="checkbox"/> Other: |

References

¹ National Institute for Health and Clinical Excellence. Cancer Service Guideline. Improving outcomes in haemato-oncology cancer. October 2003.

² Department of Health: Specialised Services National Definition Set: 2 specialised services for blood and marrow transplantation (all ages). February 2007.

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- ⁴ National Organisation for Rare Disorders (NORD). Myelodysplastic syndromes. Available at: http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Myelodysplastic%20Syndromes (accessed 30.1.08).
- ⁵ Office for National Statistics. Cancer Statistics: registrations of cancer diagnosed in 2004, England. Series MB1 No.35.
- ⁶ Office for National Statistics. Mortality statistics in 2005, England and Wales. Series DH2 No.32.
- ⁷ Kantarjian H, Oki Y, Garcia-Manero G. *et al.* Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood*. 2007; 109:52-57.
- ⁸ Kantarjian H, Issa JP, Rosenfeld CS *et al.* Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer*. 2006;106:1794-1803.
- ⁹ ClinicalTrials. Low-dose decitabine compared with standard supportive care in treating older patients with myelodysplastic syndrome. Available at: <http://clinicaltrials.gov/show/NCT00043134> (Accessed 25/4/08).
- ¹⁰ ClinicalTrials. A study of decitabine given to adults with advanced-stage myelodysplastic syndromes. Available at: <http://clinicaltrials.gov/ct2/show/NCT00260065?term=NCT00260065&rank=1> (Accessed 25/4/08).

The National Institute for Health Research National Horizon Scanning Centre Research Programme is funded by the Department of Health.

The views expressed in this publication are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health

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