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Decitabine
In Myelodysplastic Syndromes

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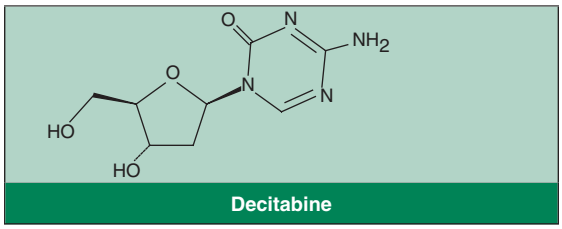
Contents

Abstract

- Decitabine is a hypomethylating agent. Its action in DNA leads to the reactivation of tumour suppressor genes and the subsequent differentiation of cancer cells.
- In a randomised, phase III trial in patients (n = 170) with myelodysplastic syndromes (MDS), intravenous decitabine (45 mg/m^2/day for 3 consecutive days every 6 weeks) combined with supportive care achieved a higher response rate (including eight complete and seven partial responses) than supportive care alone, which achieved no responses (17% vs 0%; $p < 0.001$).
- The median times to response and duration of response were 3.3 and 10.3 months in the phase III trial.
- In three phase II studies in patients (n = 29–87) with MDS treated with decitabine (40 or 50 mg/m^2/day for 3 days every 5–6 weeks), the percentage of patients achieving a complete or partial response or an improvement ranged from 26% to 49%, and the median duration of response or improvement ranged from 4.9 to 8.3 months.
- The main adverse event associated with decitabine is myelosuppression.

Features and properties of decitabine (Dacogen™)	
Indication	
Myelodysplastic syndromes (MDS)	
Mechanism of action	
Hypomethylating agent	
Dosage and administration	
Dosage	15 mg/m^2 over 3 hours every 8 hours for 3 consecutive days
Route of administration	Intravenous
Frequency of administration	Every 6 weeks
Pharmacokinetic profile (single dose of 15 mg/m^2 administered over 3 hours in adult MDS and acute myeloid leukaemia patients; mean values)	
Maximum plasma concentration	79 ng/mL
Area under the plasma concentration-time curve from time 0 to infinity	170 ng • h/mL
Volume of distribution at steady state	148 mL/kg
Elimination half-life	35 minutes
Adverse events	
Neutropenia, thrombocytopenia, anaemia, fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhoea, hyperglycaemia	



Decitabine

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterised by ineffective haematopoiesis resulting in peripheral cytopenias and a high risk of progression to acute myeloid leukaemia (AML).[1] The incidence of MDS is about 5 cases per 100 000 in the general population of the US, but it occurs in 22–45 cases per 100 000 in individuals aged >70 years.[2] The median age at diagnosis is 65–70 years.[2]

To aid in the diagnosis and classification of MDS, the French, American and British (FAB) consensus conference of haematologists and haematopathologists categorised the condition into five subtypes based on morphological criteria.[2] Later, an alternative classification system was developed by the WHO.[2] To improve the clinical and prognostic value of these systems, an International Prognosis Scoring System (IPSS) was developed.[3] This system defines critical prognostic features of MDS, including the presence of cytogenetic abnormalities, the percentage of bone marrow myeloblasts and number of cytopenias, as well as age and sex. Based on the weighting of these variables, patient risk for developing AML and for survival can be classified into low, intermediate-1, intermediate-2 and high.[3]

Because MDS generally affects elderly patients, treatment can be complicated and needs to be individualised for each patient.[2] Currently, standard treatment is supportive care, including observation, red blood cell (RBC) or platelet infusions, antibacterials and cytokine therapy.[2] High-intensity therapy using intensive induction chemotherapy or haematopoietic stem cell transplantation may achieve long-term responses, but is associated with a higher risk of treatment-related morbidity and mortality than supportive care.[2]

Recent research into MDS and other haematological malignancies has focused on epigenetic therapy.[4] Epigenetic gene silencing plays a role in the development of various cancers, including some haematological malignancies. For example, DNA hypermethylation in gene promoter regions can cause inappropriate silencing of tumour suppressor genes.[5] In MDS, *p15*, which is involved in cell cycle regulation, is often hypermethylated.[5] Pharmacological inhibition of aberrant methylation can reactivate the expression of silenced genes.[5]

Decitabine (Dacogen™)[1] was first synthesised in the early 1960s and was shown to be cytotoxic at high doses (approximately ≥750 mg/m^2/course[6]).[7] More recently, studies found that low-dose decitabine (≈50–300 mg/m^2/course[6]) acts as an epigenetic modifying agent and clinical development was refocused on MDS, AML and chronic myeloid leukaemia.[7] This article reviews the pharmacological properties of intravenous decitabine monotherapy and its clinical efficacy and tolerability in adults with MDS.

1. Pharmacodynamic Profile

Decitabine is a cytosine analogue with potent antileukaemic activity.[8] The pharmacodynamic profile of decitabine has been reviewed elsewhere.[4,7,8] This section provides a brief overview of the pharmacodynamic properties of decitabine relevant to its use in the treatment of patients with MDS.

- Inactivation of tumour suppressor genes by DNA hypermethylation plays a role in MDS.[8] Decitabine is incorporated into DNA, which traps DNA methyltransferase (DNMT), causing marked hypomethylation.[8] As a result, tumour suppressor genes are reactivated, leading to cancer cell differentiation.[8]
- DNA methylation occurs primarily at cytosine residues contained within the dinucleotide sequence cytosine phosphoguanine (CpG). According to anal-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ysis of DNA extracted from the blood of patients with MDS receiving either low-dose decitabine or supportive care,[9] methylation levels correlated with the existence of a CpG island methylator phenotype in MDS, which was associated with a poor prognosis and a risk of developing leukaemia.[9] There was no correlation between baseline methylation and response to decitabine treatment. Patients receiving decitabine demonstrated a reduction in methylation over time.[9]

- Treatment with low-dose decitabine produced marked (up to 70%) genome-wide demethylation in 5 of 7 patients with MDS.[10] In this study, bone marrow mononuclear cells were collected from patients receiving decitabine, and genomic methylation levels were analysed using micellar electrokinetic chromatography.[10]
- Hypomethylation induced by decitabine therapy led to a high level of apoptosis and death of neoplastic cells and a reduction in the proliferation of leukaemic cells.[11] For example, after 3 months, there was a significant increase compared with baseline in apoptosis of CD34+ cells in the blood of MDS patients receiving low-dose decitabine plus supportive care, but not in those receiving supportive care alone ($p = 0.01$), as measured in bone marrow and peripheral blood samples.[11]
- Hypermethylation of *p15*^{INK4B}, an inhibitor of cyclin-dependent kinases, was reversed in patients with MDS who responded to decitabine therapy.[12] Examination of bone marrow mononuclear cells collected from patients before and after treatment with at least one course of low-dose decitabine, revealed that 9 of 12 patients with hypermethylation had a decrease in *p15* methylation, which was associated with a clinical response.[12]
- As well as DNA demethylation, decitabine also appears to exert a methylation-independent effect.[13] Using microarray and subsequent reverse transcriptase-polymerase chain reaction analysis, 4 of 5 analysed decitabine-induced genes lacked any DNA methylation in their upstream regions.[13]
- Furthermore, in a series of AML cell lines, decitabine caused induction of p21^{WAF} (a cyclin-dependent kinase inhibitor), which correlated with apoptosis of AML cells.[14] The decitabine-induced induction of p21 was not a result of direct demethylation but was mediated by re-expression of the 5′-methylated tumour-suppressor gene *p73*, a transcriptional regulator of p21.[14]
- Decitabine induced trilineage haematological responses as well as causing normalisation of the bone marrow and peripheral blood in some patients with MDS.[15] Decitabine (45 mg/m^2/day [in 3 divided doses/day; n = 6] or 50 mg/m^2/day [continuous infusion; n = 4], both for 3 consecutive days) resulted in a marked increase in neutrophils, platelets and haemoglobin compared with pretreatment values in half of the patients.[15] This improvement was accompanied by a reduction of bone marrow and peripheral blood myeloblasts in five patients.[15]
- Furthermore, a rise in platelet count preceded a good trilineage response in patients with MDS (n = 162) receiving decitabine (40–50 mg/m^2/day for 3 days).[16] In an intent-to-treat analysis, 45% of patients experienced an increase in platelet count compared with baseline after one cycle of therapy.[16]
- Low-dose decitabine was as effective as, or more effective than, higher dosages in a phase I study of prolonged-exposure schedules in patients with haematological malignancies (including some with MDS).[17] Dosages included decitabine 5–20 mg/m^2 given intravenously over 1 hour each day for 10 days (5 days a week for 2 consecutive weeks), and decitabine 15 mg/m^2 daily for 15 or 20 days. Responses were seen at all dose levels but decitabine at 15 mg/m^2 for 10 days appeared to achieve the best treatment effect.[17]

2. Pharmacokinetic Profile

The single- and multiple-dose pharmacokinetic profile of intravenous decitabine in MDS patients has been evaluated in a single study.[18] Twelve patients, six with MDS and six with AML, received decitabine at 15 mg/m^2 given over 3 hours every 8 hours for 3 days; five of the twelve patients received a second cycle after 6 weeks.[18]

- After a single 3-hour infusion of decitabine at 15 mg/m^2 in ten patients, the mean maximum plasma concentration (C_{max}) was 79 ng/mL and the time to

C_{max} was 2.67 hours.[18] The area under the plasma concentration-time curve from time 0 to infinity (AUC_∞) was 170 ng • h/mL. C_{max} and AUC values did not change significantly during the full 3-day cycle. At the completion of the first cycle of treatment, the AUC ratio between day 3 and day 1 was 0.92.[18]

- Decitabine did not accumulate in plasma during treatment cycles.[18] In patients who received decitabine for two cycles, the mean C_{max} for cycle 1 was 49.0 ng/mL and for cycle 2 was 62.7 ng/mL. These values were not significantly different, indicating unchanged pharmacokinetic parameters during the second cycle.[18]
- The mean volume of distribution at steady state after a single infusion of decitabine 15 mg/m^2 was 75.8 L/m^2, and the mean total plasma clearance was 122 L/h/m^2 indicating extensive clearance including extrahepatic elimination. The mean elimination half-life was about 35 minutes (0.58 hours).[18]

3. Therapeutic Efficacy

The efficacy of decitabine in the treatment of MDS has been evaluated in a randomised, nonblind, multicentre, phase III trial[19,20] as well as several noncomparative phase II studies.[21-24] Data are from fully published papers[19-21,23] except for two abstracts[22,24] and a poster[22] covering phase II data.

In the phase III study, patients aged >18 years with MDS were randomised to receive supportive care alone (n = 81) or intravenous decitabine 45 mg/m^2/day (15 mg/m^2 given over 3 hours and repeated every 8 hours) for 3 consecutive days every 6 weeks (n = 89).[19] Supportive care included RBC and/or platelet transfusions and haematopoetic colony-stimulating factors. Patients continued in the study until disease progression or, in the case of a complete response, until they had received two further cycles of treatment.[19]

Evaluations of response included a blinded central review of bone marrow aspirates and biopsies.[19] Responses were defined according to the International Working Group criteria.[25] For patients to achieve a complete response, bone marrow evaluation needed to show <5% myeloblasts with normal maturation of all cell lines and no evidence of dysplasia.[19] Peripheral blood evaluation needed to show haemoglobin >11 g/dL, neutrophils $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L and 0% blasts. A partial response was defined as all of the complete response criteria except blasts showed a decrease ≥50% over pretreatment levels but remained >5% on bone marrow evaluation, or MDS FAB classification was less advanced than before treatment. Absolute values in all criteria needed to have persisted for at least 2 months.[19]

The primary efficacy endpoints were overall response rate (i.e. complete plus partial response) and time to AML or death.[19] Secondary endpoints included haematological improvement and cytogenetic response rates (both are defined in the International Working Group Report[25]), transfusion requirements, survival and quality of life (QOL).

Baseline characteristics were similar in each group.[19] Overall, about two-thirds of patients were male. The median time from diagnosis of MDS to commencing the study was 29 weeks for the decitabine group and 35 weeks for the supportive care arm (p = 0.9). Approximately 14% of patients had secondary MDS, the remainder having *de novo* disease. The IPSS risk classification was intermediate-1 in ≈31%, intermediate-2 in ≈44% and high in 26% of patients. Each patient was also classified into one of the five subgroups of the FAB classification system: refractory anaemia (RA) [≈14%], RA with ringed sideroblasts (RARS) [≈7%], RA with excess blasts (53%), RA with excess blasts in transformation (≈18%) and chronic myelomonocytic leukaemia (>1000 monocytes/μL blood) [≈9%].[19] Patients had a WHO performance status of 0–2.[19]

In the phase II studies, decitabine 45 or 50 mg/m^2/day was given for 3 consecutive days every 5–6 weeks, and patients generally received a maximum of eight cycles.[21,22] Primary endpoints included response rate, as defined by the International Working Group criteria[25] (summarised earlier in this section) and improvement, which was defined as a decrease of ≥50% in transfusion requirements, as well as an improvement in one or two cell lineages of the peripheral cell counts that were not sufficient

to qualify for a partial response.[21] Phase II trials also evaluated response duration, survival and best haematological response.[21,22] Patient baseline characteristics were generally similar to those of the phase III study.[21,22]

Phase III Trial

- The overall response rate in the intent-to-treat population was significantly higher in patients receiving decitabine (45 mg/m^2/day for 3 days every 6 weeks) plus supportive care than in those receiving supportive care alone (17% vs 0%; $p < 0.001$).[19] In the decitabine group, eight patients had a complete response and seven achieved a partial response. The median time to response was 3.3 months (≈2 cycles of therapy), and the median duration of response was 10.3 months.[19] In an additional analysis, in patients considered evaluable for response (i.e. pathologically confirmed MDS at baseline and received ≥2 cycles of treatment) the ORR was 21% (12/56 patients).[26]
- The median time to AML or death was 4.3 months longer in patients receiving decitabine plus supportive care than in those receiving supportive care alone (12.1 vs 7.8 months), although this difference did not reach statistical significance ($p = 0.16$) [figure 1].[19] The probability of progression to AML or death was 2-fold higher in patients not receiving decitabine (hazard ratio 0.58; 95% CI 0.37, 0.91), based on a Cox proportional hazards model adjusted for IPSS classification and type of MDS.[19]
- Overall response rates were higher in patients receiving decitabine plus supportive care than in those receiving supportive care alone in almost all subgroups, including all IPSS prognostic groups, most FAB subtypes, those with *de novo* or secondary MDS and those who were or were not previously treated. Response rates ranged from 13% to 21% across all decitabine-treated subgroups compared with no responses in the supportive care only subgroups (excluding the small RARS subgroup, in which the overall response rate was 0% in both arms).[19]
- For example, in patients categorised as high risk (IPSS), an overall response was achieved in 17% (4 of 23) of decitabine recipients but none of the 21 patients in the supportive care group.[19] Among these subgroups, a statistically significant difference compared with supportive care alone was achieved for decitabine-treated patients in the IPSS intermediate-2 subgroup ($p < 0.011$), those with no prior therapy and those with *de novo* MDS status (both $p < 0.01$).[19]
- Further subgroup analyses demonstrated that decitabine-treated patients had a significantly longer time to AML or death than those receiving supportive care alone in patients with IPSS intermediate-2/high risk (12 vs 6.8 months; $p = 0.03$), those with IPSS high risk (9.3 vs 2.8 months; $p = 0.01$) and those with *de novo* MDS (12.6 vs 9.4 months; $p = 0.04$).[19] The difference did not reach statistical significance in treatment-naive patients (12.3 vs 7.3 months; $p = 0.08$). In patients who achieved an overall response (n = 15) in the decitabine group, the median time to AML or death was 7.8 months longer than in nonresponders from either group (n = 155) [17.5 vs 9.8 months; $p = 0.01$).[19]
- Median survival was not significantly different between the decitabine and the supportive care groups (14 vs 14.9 months). Survival was signifi-

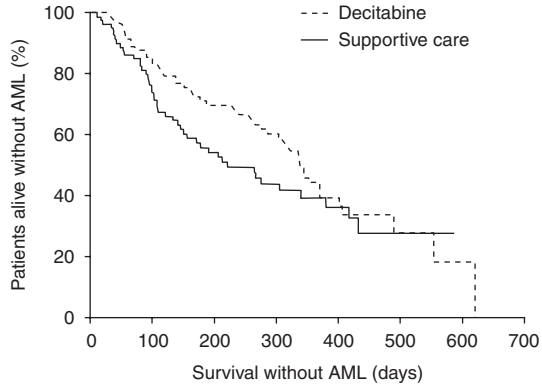


Fig. 1. Time to acute myeloid leukaemia (AML) or death in patients with advanced myelodysplastic syndrome. Intent-to-treat results are taken from a randomised, nonblind, multicentre, phase III trial in which patients received intravenous decitabine (15 mg/m^2 over 3 hours every 8 hours for 3 consecutive days every 6 weeks) plus supportive care (n = 89) or supportive care alone (n = 81).[19] $p = 0.16$ for 2-sided log-rank test for homogeneity of survival distributions. (Reproduced from Seminars in Hematology, 42, Saba and Wijermans, Decitabine in Myelodysplastic Syndromes, S23-31,[20] Copyright [2005], with permission from Elsevier).

cantly longer among responders to decitabine than among nonresponders (23.5 vs 13.7 months; p = 0.007).[19]

- Haematological improvement, excluding patients with a complete or partial response, was observed in 13% of patients in the decitabine group compared with 7% of those receiving supportive care alone.[19] Rates of overall improvement (complete plus partial responses plus haematological improvement) were 30% versus 7% (p < 0.001).[19]
- Major cytogenetic responses (i.e. no detectable cytogenetic abnormality on follow-up despite baseline abnormalities) were observed in 9 of 26 (35%) patients in the decitabine group compared with 2 of 21 (10%) patients in the supportive care group.[19]
- Fewer patients in the decitabine plus supportive care group received erythropoietic growth factors than in the supportive care group (20% vs 41%). In addition, during the study period, the percentage of patients who became RBC transfusion independent increased in the decitabine group (e.g. from ≈5% for cycle 1 to >50% for cycle 6) but did not change markedly in the supportive care arm (≈20% for both cycles 1 and 6).[19]
- Improvement in the QOL parameter global health status was numerically higher with decitabine plus supportive care than with supportive care alone after all 6 treatment cycles, although statistical significance was achieved onlyafter cycles 2 and 4 (e.g. change from baseline +29% versus −11% for cycle 4; p < 0.05; values estimated from a graph).[19] QOL assessments also found that decitabine treatment was associated with significant improvements in dyspnoea after all cycles and in fatigue after most cycles (all p < 0.05).

Phase II Trials

- In three noncomparative phase II studies (n = 29–87) of intravenous decitabine (45 or 50 mg/m^2/day for 3 days every 5–6 weeks), the percentage of MDS patients achieving a complete or partial response or an improvement ranged from 26% to 49%, and the median duration of response or improvement ranged from 4.9 to 8.3 months.[21,22] A complete response was seen in 20–28% of patients.[21,22] Haematological improvement was observed in 7–15% of patients.[22]
- In the fully published study (n = 66), median survival time from diagnosis was 22 months and from the start of decitabine therapy was 15 months.[21] For patients with an IPSS high-risk rating, median survival time from the start of treatment was 14 months. Median progression-free survival for all patients was 5.8 months.[21]
- Of 115 MDS patients from these studies who were karyotyped, 61 (53%) were found to have clonal chromosomal abnormalities prior to treatment.[27] After receiving a median of 3 courses of decitabine, 31% of the 61 patients achieved a major cytogenetic response.[27] Survival was improved in patients achieving a major cytogenetic response compared with those in whom the cytogenetically abnormal clone persisted (24 vs 11 months; p = 0.0213).[27]
- Re-treatment with decitabine achieved inferior responses to those achieved with initial exposure to the drug, according to an analysis of MDS patients treated with decitabine both initially and after relapse.[23] During initial treatment, 82% of these patients (18 of 22) had achieved a complete (12 patients; 55%) or partial (6 patients) response or haematological improvement (4 patients) after a median of six courses. During retreatment, a median of three courses was administered a median of 11 months after the final course of initial treatment.[23] A response rate of 45% (10 patients) was achieved, including just one complete response (and two partial responses and seven haematological improvements), and with a median time from second response to relapse of 4 months. Median overall survival (from first decitabine course) was 27.5 months.[23]
- Interim results from a randomised study comparing three decitabine dosing schedules incorporating low daily doses over an increased number of days per cycle (each administering a total of 100 mg/m^2/cycle and repeated every 4–6 weeks) found that intravenous decitabine 20 mg/m^2/day for 5 days was significantly more effective than intravenous decitabine 10 mg/m^2/day for 10 days or subcutane-

ous decitabine 10 mg/m^2 twice daily for 5 days (p-values not reported).[24] Overall, in 96 evaluable patients who received one course, 47% achieved a complete or partial response. Complete responses were achieved in 49% of 65 patients who received the intravenous 5-day schedule, 29% of 14 patients who received the subcutaneous 5-day schedule, and 24% of 17 patients who received the intravenous 10-day schedule.[24]

4. Tolerability

Data on the tolerability of decitabine in patients with MDS come from the phase III study[19] and several phase II studies[21,22,24] (see section 3 for study design details).

- Across all studies, the most common adverse event was myelosuppression (including neutropenia, thrombocytopenia and anaemia[26]), which may be associated with febrile neutropenia and infection.[19,21,22,24] The incidences of grade 3/4 haematological adverse events that occurred in >5% of patients in the phase III trial are summarised in figure 2. The incidence of myelosuppression adverse events appeared to decrease over the first four decitabine treatment cycles in this trial, although they remained frequent.[19]

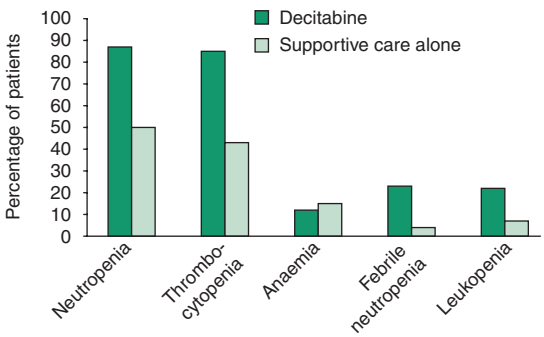


Fig. 2. Haematological tolerability profile of patients with myelodysplastic syndrome in a nonblind, multicentre, phase III study.[19] Patients were randomised to receive intravenous decitabine (15 mg/m^2 over 3 hours every 8 hours for 3 consecutive days every 6 weeks) plus supportive care (n = 83) or supportive care alone (n = 81). Grade 3/4 adverse events that occurred in >5% of patients are shown. Levels of significance were not reported.

- Overall, the most frequent non-haematological adverse events with decitabine in the phase III trial (regardless of grade) included fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhoea and hyperglycaemia (all >30% of patients).[26]
- In the fully published phase II study (n = 66), grade 3/4 adverse events, and grade 2 toxicities that required hospitalisation, occurring in ≥5% of patients in the decitabine group were fever (27% vs 14% in the supportive care group), infection (20% vs 10%), sepsis (11% vs 4%), neutropenia (12% vs 7%), anaemia (11% vs 6%), thrombocytopenia (5% vs 2%) and gastrointestinal disturbance (6% vs 2%).[21]
- In the same study, the treatment-related mortality rate was 7% and was generally associated with pancytopenia and infection.[21]

5. Dosage and Administration

The recommended dosage of intravenous decitabine is 15 mg/m^2 given over 3 hours and repeated every 8 hours for 3 consecutive days every 6 weeks.[19] It is recommended that patients receive at least 4 cycles.[19]

Local prescribing information should be consulted for dosage adjustments based on haematological recovery time between cycles, recommendations for specific populations, contraindications and precautions.

6. Decitabine: Current Status in the Treatment of Myelodysplastic Syndromes

The US FDA has approved decitabine injection for use in the treatment of MDS.[28] In a well designed phase III trial, the addition of decitabine to supportive care significantly improved response rates compared with supportive care alone in patients with MDS.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on

any comments received were made on the basis of scientific and editorial merit.

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