Decitabine in the treatment of myelodysplastic syndromes

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Abstract: Patients with myelodysplastic syndromes (MDS) are challenging to treat, given the advanced median age and comorbidities of the population. For most patients, the standard therapy is supportive care, including broad-spectrum antibiotics, red blood cell/platelet transfusions, and growth factors. Decitabine, a hypomethylating agent that allows for the re-expression of tumor suppressor genes, represents an exciting new treatment option for MDS patients. In phase 2 and 3 studies, decitabine has been associated with durable responses in MDS patients and delayed time to acute myeloid leukemia (AML) transformation or death compared with supportive care. Decitabine has been shown to be well tolerated with a toxicity profile expected for this class of agent. Recent studies also suggest that lower dose schedules of decitabine may result in additional improvements in response. As more is learned about the mechanism of hypomethylating agents, new roles are emerging for decitabine in combination therapy for MDS and in other hematologic malignancies such as AML.

Keywords: decitabine, myelodysplastic syndromes, hypomethylating agent, DNA methyltransferase inhibitor, gene silencing

Myelodysplastic syndromes

Myelodysplastic syndromes (MDS) are a group of bone marrow disorders characterized by ineffective hematopoiesis resulting in anemia, neutropenia, and thrombocytopenia (American Cancer Society 2005; Myelodysplastic Syndromes Foundation 2006; American Cancer Society 2006). MDS can be classified as de novo, arising from no apparent cause, or as secondary, resulting from exposure to a mutagen such as chemotherapy or benzene (American Cancer Society 2005; Aplastic Anemia & MDS International Foundation 2005). Chromosomal abnormalities are common in both types of MDS (Kurzrock 2002; List et al 2004; American Cancer Society 2005; American Cancer Society 2006). In patients with de novo MDS, chromosomal abnormalities have been reported in approximately 40%–70% of cases, whereas in patients with secondary MDS, chromosomal abnormalities are observed in almost 95% of cases (List et al 2004). MDS occurs primarily in the elderly and is rare in young adults (Williamson et al 1994; Aul et al 1998; American Cancer Society 2005; American Cancer Society 2006).

Although the exact number of MDS cases is unknown owing to the lack of a central United States registry, it is estimated that, in the general population, MDS occurs in 5 per 100,000 people (National Comprehensive Cancer Network 2006). Estimates range between 10,000 and 20,000 new cases of MDS per year in the United States (American Cancer Society 2005; Aplastic Anemia & MDS International Foundation 2005). The number of MDS cases is believed to be increasing as a result of the aging population and the increased survival rate of patients who have received chemotherapy (American Cancer Society 2005).

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The greatest risk factor for MDS appears to be advancing age, with 80%–90% of all patients over 60 years old (American Cancer Society 2005). Other risk factors for MDS are previous chemotherapy, exposure to environmental toxins, tobacco and cigarette smoke, congenital disorders, familial disorders, and being of male gender (American Cancer Society 2005). Clinical symptoms may include fatigue, weakness, and serious infections; however, approximately half of MDS patients are asymptomatic at the time of initial diagnosis and are diagnosed only after routine laboratory tests show abnormalities (Hofmann and Koeffler 2005; American Cancer Society 2005; Aplastic Anemia & MDS International Foundation 2005). Although MDS can eventually result in neutropenia and/or thrombocytopenia, anemia is the most common characteristic at the time of initial diagnosis. In the early course of the disease, a hemoglobin value of less than 10 g/dL has been observed in approximately 80% of patients (Hofmann and Koeffler 2005).

Prognosis can depend on many variables, including morphology, number of cytopenias, blast count, and cytogenetics. Left untreated, the median survival ranges from 0.4 years for high-risk MDS patients to 5.7 years for low-risk MDS patients (Greenberg et al 1997). In the majority of MDS patients, death typically results from complications of bone marrow failure, such as chronic anemia, infections, or severe bleeding (Kurzrock 2002; Myelodysplastic Syndromes Foundation and Bennett 2006). Approximately one-third of adult MDS patients progress to acute myeloid leukemia (AML), with a median survival of 6–12 months (Ganser and Hoelzer 1992; Greenberg et al 1997).

Classification systems

At the present time there are two MDS classification systems that have been used to determine expected median survival and median time to AML transformation. The French-American-British (FAB) Co-operative Group Classification recognizes five subgroups of MDS based on cell morphology and the percentage of blasts (Bennett et al 1982). In order to improve the prognostic value, the World Health Organization (WHO) subsequently made modifications to FAB that included the reduction of the blast threshold for the diagnosis of AML and refinements of the categories of refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS) (Vardiman et al 2002).

There has also been the development of a widely used prognostication tool, the International Prognostic Scoring System (IPSS), which takes into account cytogenetics and number of cytopenias as well as morphology (Greenberg et al 1997; Kurzrock 2002). The IPSS scoring system subdivides MDS into four distinct subgroups for predicting survival and risk of transformation to AML (Table 1) (Greenberg et al 1997).

Table 1 International prognostic scoring system (IPSS) score and prognosis

	Score[a]				
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2.0**
Marrow blasts (%)	<5	5–10	—	11–20	21–30
Karyotype[b]	Good	Intermediate	Poor	NA	NA
Cytopenias[c]	0/1	2/3	NA	NA	NA

Combined prognosis score	**IPSS subgroup**	**Median time to AML transformation, 25% of patients (yrs)**	**Medial survival (yrs)**
0	Low	9.4	5.7
0.5–1.0	Intermediate-1	3.3	3.5
1.5–2.0	Intermediate-2	1.1	1.2
>2.5	High	0.2	0.4

[a]Based on the combined score, four risk groups have been identified: low (combined score: 0), intermediate-1 (combined score: 0.5–1), intermediate-2 (combined score: 1.5–2), and high (combined score: >2).
[b]Good: diploid, -Y (loss of the Y chromosome); del(5q), del(20q), deletion of 5q and 20q chromosomes; poor: complex, chromosome 7 abnormalities; intermediate: others.
[c]Hemoglobin <10g/dL, neutrophils $<1.5 \times 10^9$/L, platelets $<100 \times 10^9$/L.
NA, not applicable; AML, acute myeloid leukemia.
Source: Adapted, with permission, from "International scoring system for evaluating prognosis in myelodysplastic syndromes" (Greenberg et al 1997) p2085. Copyright 1997 by the American Society of Hematology.

Clinical practice guidelines

Evidence-based treatment guidelines for MDS have recently been published by the Italian Society of Hematology, the United Kingdom, and the United States (National Comprehensive Cancer Network [NCCN]) (Alessandrino et al 2002; Bowen et al 2003; National Comprehensive Cancer Network. 2006). According to these guidelines, the treatment strategy for MDS should be determined by IPSS risk category, as well as age and performance status. The recently updated NCCN guidelines recommend hypomethylating agents, such as decitabine or azacitidine, for the treatment of higher risk MDS patients and for lower risk MDS patients who are nonresponsive to growth factor therapy or who are HLA-DR15 negative (National Comprehensive Cancer Network. 2006).

Treatment options

The MDS patient population presents many challenges when considering an appropriate treatment strategy, including advanced age, comorbidities, and an inability to tolerate certain types of intensive therapy. Therapy should be selected based on the patient's performance status, disease classification, IPSS score, and treatment tolerance. In patients with a low-risk or intermediate-1 IPSS score, the goals of therapy are to improve blood counts and ensure age-related quality of life (National Comprehensive Cancer Network. 2006), whereas for intermediate-2 and high-risk patients, the goals of therapy are to prolong survival and delay leukemic progression (National Comprehensive Cancer Network. 2006). The only potentially curative treatment for MDS is hematopoietic stem cell transplantation (HSCT), however, this option is available for only a small number of patients (ie, younger age, histocompatible donor, no significant comorbidities) (Alessandrino et al 2002; Bowen et al 2003; National Comprehensive Cancer Network. 2006). Some high-risk MDS patients who are not candidates for HSCT may be eligible for intensive antileukemic chemotherapy (Alessandrino et al 2002; Bowen et al 2003; National Comprehensive Cancer Network. 2006). Nevertheless, the vast majority of MDS patients are managed with supportive care, including red blood cell (RBC)/platelet transfusions, growth factors such as recombinant erythropoietin and colony-stimulating factors, and antibiotics, including broad coverage in neutropenic patients as infection occurs.

A number of emerging therapeutic options are currently being evaluated for the treatment of MDS that will, it is hoped, add to the treatment options for patients who are ineligible to receive HSCT or intensive chemotherapy. Lenalidomide, an immunomodulatory drug derived from thalidomide, has been recently approved by the Food and Drug Administration (FDA) and is indicated for the treatment of MDS in patients with chromosome 5q deletion. Other agents such as imatinib and tipifarnib are currently being evaluated in clinical trials (Cortes et al 2003; Feldman 2005; Sekeres 2005; Jabbour and Giles 2005). Some of the therapies farthest along in development are the hypomethylating agents decitabine and azacitidine, both of which have been recently approved by the FDA for the treatment of MDS.

Hypermethylation in cancer

DNA methylation is a common epigenetic modification that plays an important role in gene expression in mammalian cells (Leone et al 2002; Das and Singal 2004). As part of normal development, certain genes may be silenced through methylation of cytosine residues in their promotor regions (CpG islands). However, in some hematopoietic neoplasms including MDS, DNA hypermethylation can inactivate genes essential for the control of normal cell growth, differentiation, or apoptosis. A group of enzymes called DNA methyltransferases (DNMTs) catalyze the methylation of cytosine residues in newly synthesized DNA, thus replicating the methylation signal. In recent years, there has been interest in pharmacologic therapies that target this mechanism by inhibiting DNMT, resulting in hypomethylation of the DNA and re-expression of tumor suppressor genes. Cytosine analogues such as decitabine have been shown to inhibit DNMT and are being used against MDS, as well as AML and other cancers (Leone et al 2002; Das and Singal 2004).

Multiple genes appear to be hypermethylated in MDS, including $p15^{INK4B}$, which encodes a cell-cycle inhibitor. Evidence suggests that $p15^{INK4B}$ methylation is correlated with blastic bone marrow involvement and that it increases during disease progression to AML (Quesnel et al 1998; Quesnel and Fenaux 1999). Methylation of the $p15^{INK4B}$ gene may allow leukemic cells to escape the inhibitory signals in the bone marrow (Quesnel et al 1998; Quesnel and Fenaux 1999). Decitabine treatment has been shown to reverse hypermethylation of $p15^{INK4B}$, allowing for re-establishment of normal $p15^{INK4B}$ protein expression (Daskalakis et al 2002). In addition, hypomethylation of $p15^{INK4B}$ has been associated with hematologic response, supporting pharmacologic demethylation as a possible mechanism for clinical response (Daskalakis et al 2002).

Decitabine is believed to have a dual mechanism of action depending on dose. At both lower and higher doses, decitabine incorporates into DNA; however, at

higher doses, decitabine inhibits cell proliferation through nonreversible covalent linking with DNA methyltransferase and blocking of DNA synthesis (Leone et al 2002). At lower doses, decitabine induces hypomethylation, thereby promoting cell differentiation, re-expression of tumor suppressor genes, stimulation of immune mechanisms, and suppression of tumor growth (Leone et al 2002; Mund et al 2005).

Description and structure of decitabine

Decitabine (5-aza-2'-deoxycytidine) is a cytosine analogue modified in position 5 of the pyrimidine ring (Figure 1). Decitabine is slightly soluble in ethanol/water (50/50), methanol/water (50/50), and methanol; sparingly soluble in water; and soluble in dimethylsulfoxide (DMSO). Decitabine (Dacogen™ for Injection) is a white to almost-white sterile lyophilized powder supplied in a clear, colorless glass vial (Dacogen 2006).

Pharmacokinetics

Decitabine distributes extensively throughout human tissues. In a phase 1 pharmacokinetic study of decitabine in 21 patients with advanced solid tumors, the mean value of volume of distribution was found to be 4.59 L/kg ± 1.42 (van Groeningen et al 1986). Although the exact route of elimination and metabolic fate of decitabine is unknown in humans, high total body clearance values and a total urinary excretion of less than 1% of the administered dose suggest that decitabine is eliminated rapidly and primarily through enzymatic metabolism (van Groeningen et al 1986).

In a more recent pharmacokinetic phase 1 study, 16 patients with MDS/AML were administered decitabine at a dose of 15 mg/m^2 as a 3-hour infusion every 8 hours for 3 consecutive days of a 6-week cycle for two cycles (Cashen et al 2005). Preliminary results suggest that repeated administration of decitabine does not result in systemic accumulation of the drug. For the five patients who received decitabine for two cycles, maximum concentration (C_{max}) values for

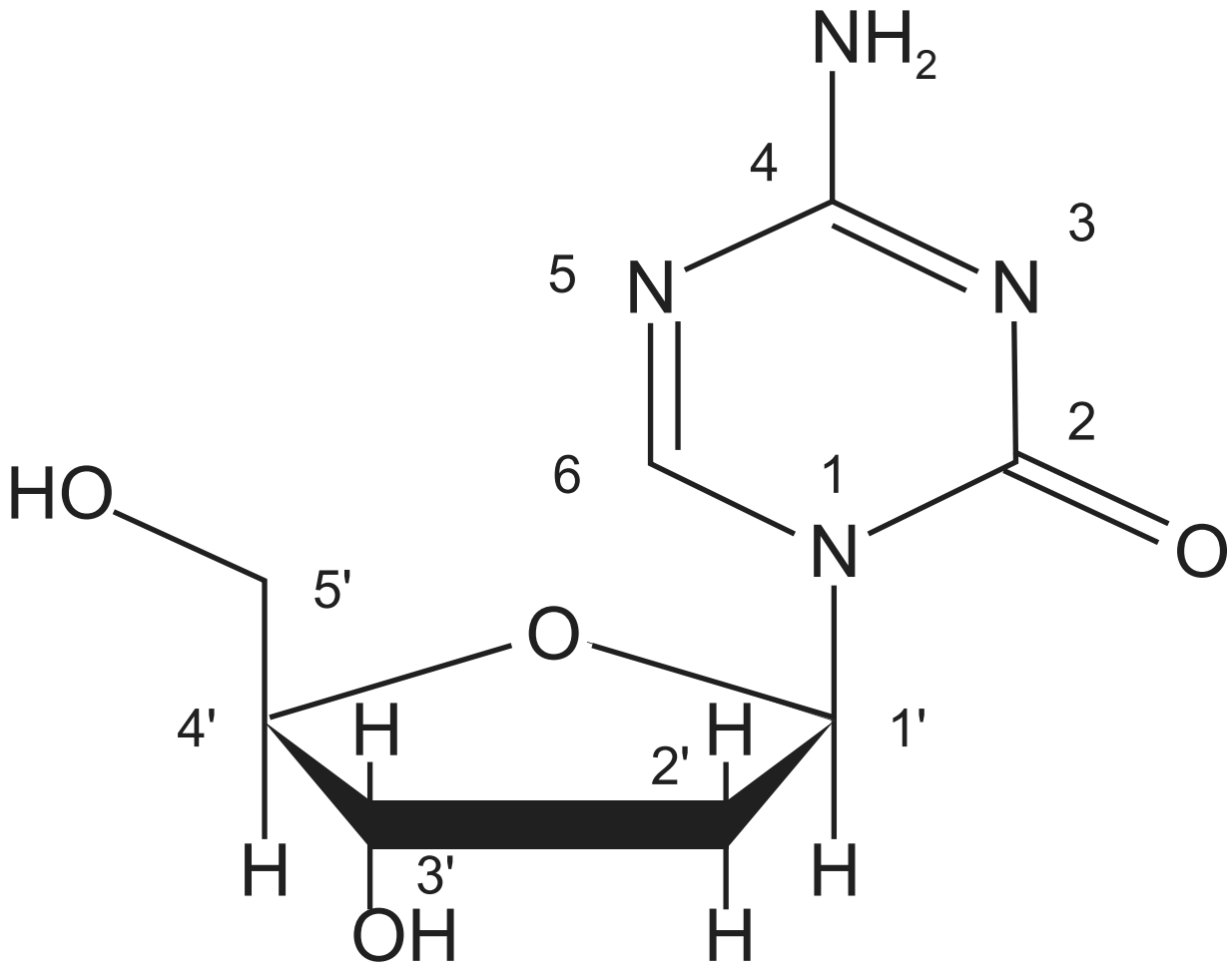

Figure 1 Decitabine structure.

Cycle 1 (49.0 ± 22.2 ng/mL) and Cycle 2 (62.7 ± 45.2 ng/mL) were comparable, suggesting that decitabine pharmacokinetics remain unchanged from cycle to cycle.

Clinical studies of decitabine

Phase 2 studies of decitabine in MDS patients yielded encouraging response rates, including overall responses (complete response [CR] + partial response [PR]) of 26%–45% and complete responses of 21%–28% (Wijermans et al 1997; Wijermans et al 2000; Saba et al 2005; Saba and Wijermans 2005). These results led to a North American, multicenter phase 3 study of decitabine compared with supportive care in 170 MDS patients, which formed the basis for the FDA approval of decitabine (Saba et al 2004; Kantarjian et al 2006). Patients were stratified by IPSS risk group and type of MDS (de novo or secondary) and randomly assigned to receive either supportive care alone or decitabine at a dose of 15 mg/m^2 as a 3-hour infusion every 8 hours for 3 days, repeated every 6 weeks, plus supportive care. Primary endpoints were overall response rate (ORR) and time to AML transformation or death. Responses were assessed using the International Working Group (IWG) criteria (Cheson et al 2000), which defined a CR as normalization of peripheral counts and bone marrow for at least 8 weeks with serial bone marrow blasts less than 5% without dysplastic changes, hemoglobin greater than 11 g/dL, a neutrophil count 1.5×10^9/L or greater, and a platelet count of 100×10^9/L or greater. A PR was defined similarly to CR except for the reduction of ≥50% of blasts that remained above 5%, or a downgrade in the FAB criteria. Response criteria had to be met for at least 8 weeks. The study design dictated that patients be removed from therapy after two cycles of a maintained CR.

The results of the phase 3 study indicate that decitabine is clinically effective in patients with MDS. Patient baseline characteristics were well balanced between the two study arms. Responses were defined according to strict IWG criteria (Cheson 2000). The ORR of patients in the decitabine arm was 17% compared with 0% in the supportive care only arm ($p < 0.001$) (Table 2). In decitabine-treated patients considered evaluable for response (ie, those patients with pathologically confirmed MDS at baseline who received at least two cycles of treatment), the ORR was 21% (12/56) (McKeage and Croom 2006). Responses were observed across all IPSS risk groups and were found to be durable, with a median duration of response of 10.3 months (Table 2). Median time to first response (PR or CR) was 3.3 months (Table 2). Hematologic improvement (HI) was observed in an additional 13% of patients in the decitabine group versus 7% in the supportive care arm. The overall improvement rate for patients receiving decitabine was 30% versus 7% for patients receiving supportive care. Patients in the decitabine arm had a median time to AML or death that was 4.3 months greater than that of patients in the supportive care only arm ($p = 0.16$) (Figure 2A). When patient subgroups were analyzed, patients receiving decitabine experienced a longer time to AML or death than patients receiving supportive care only (treatment-naïve [12.3 vs 7.3 months; $p = 0.08$] [Figure 2B], IPSS risk of intermediate-2/high-risk patients [12.0 vs 6.8 months; $p = 0.03$] [Figure 2C], IPSS high-risk patients [9.3 vs 2.8 months; $p = 0.01$], or de novo MDS [12.6 vs 9.4 months; $p = 0.04$]).

All responders in the phase 3 study, defined as patients achieving a CR or PR, became RBC and platelet transfusion independent in the absence of growth factors during the time of the response (Saba et al 2004; Saba and Wijermans 2005; Kantarjian et al 2006). The percentage of patients in the decitabine arm who became RBC transfusion independent increased with increased number of treatment cycles, while the percentage of patients on supportive care who required RBC transfusions did not change (Figure 3). All eight

Table 2 Response to decitabine (ITT) using the FDA approved dose of 15 mg/m^2 over 3 hours every 8 hours × 3 days every 6 weeks (Adapted, with permission, from Kantarjian et al (2006))

International working group response rate, onset, and duration	Decitabine (n = 89)	Supportive care (n = 81)
Overall response rate (CR + PR)	15(17%)*	0(0%)
CR	8(9%)	0(0%)
PR	7(8%)	0(0%)
HI	12(13%)	6(7%)
*p-value < 0.001 from two-sided Fisher's exact test		
Onset and duration of response (months)		
Median time to (CR + PR) response	3.3(2.0 – 9.7)	
Median duration of (CR + PR) response	10.3(4.1 – 13.9)	N/A

Abbreviation: ITT, intention to treat; CR, complete response; PR, partial response; HI, hematologic improvement.

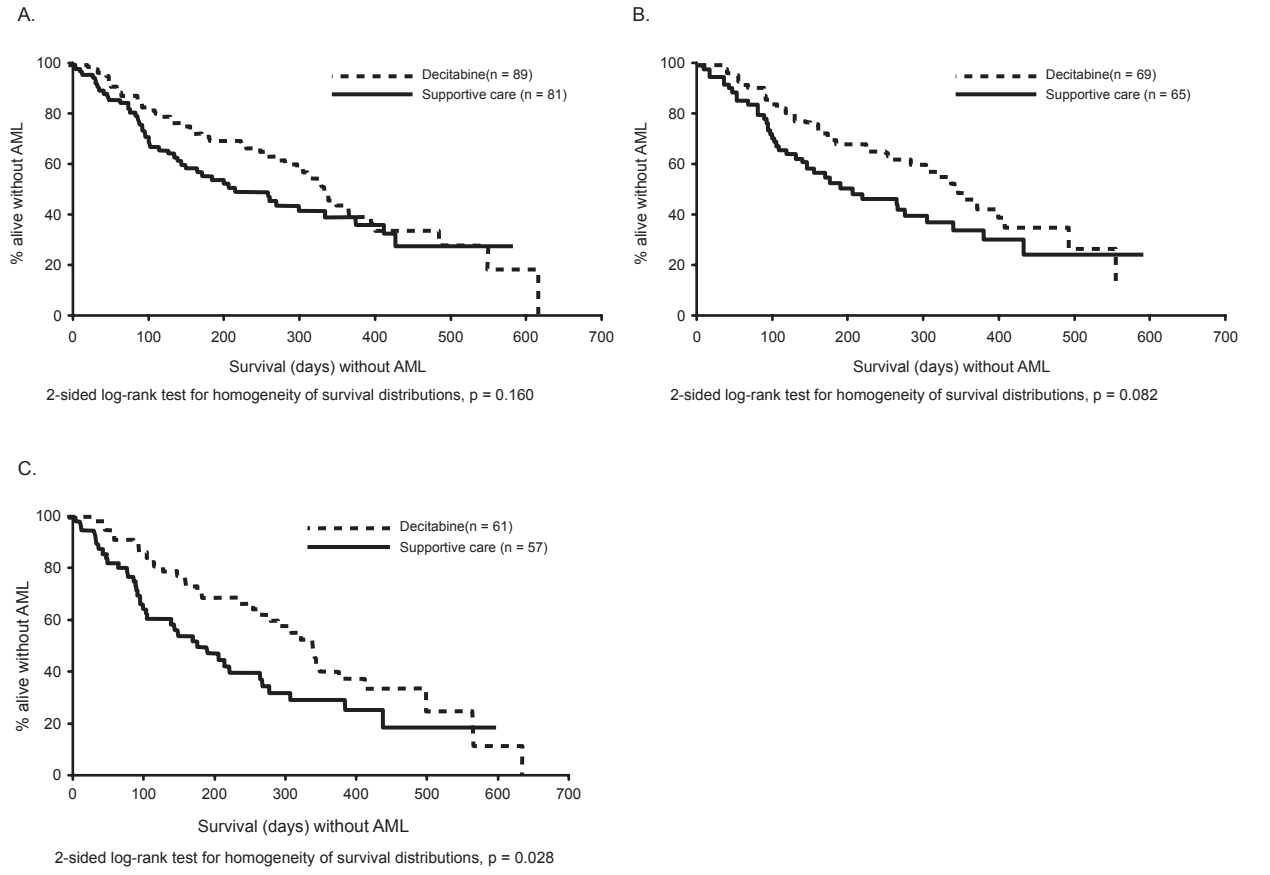

Figure 2 Time to acute myeloid leukemia (AML) or death: (**A**) all patients; (**B**) treatment-naïve patients; (**C**) International Prognostic Scoring System subgroups intermediate-2 to high-risk patients. (Reprinted, with permission, from Kantarjian et al 2006).

responders who had cytogenetic abnormalities at baseline and were evaluable for cytogenetic response achieved a cytogenetic response (seven major responses and one minor response). The median number of cycles delivered was three, with 43 of 89 patients receiving two or more cycles. Of the 15 patients who responded after decitabine treatment, the median number of courses was six. In contrast, the median number of cycles in the phase 2 studies was four, which may in part explain the slightly higher response rates in the phase 2 studies (Saba et al 2005). The authors of the phase 3 study speculate that greater benefit may have been observed if the study design had allowed patients to continue receiving decitabine therapy for a longer period of time.

Safety data were evaluated for 83 patients treated with decitabine and 81 patients who received supportive care only. Overall, decitabine therapy was well tolerated with manageable adverse effects. The most common adverse effects included myelosuppression (neutropenia, thrombocytopenia, and anemia), pyrexia, fatigue, nausea, cough, petechiae, diarrhea, and constipation (Table 3). Febrile neutropenia occurred in 28% of patients who received decitabine. The authors noted that neutropenia, thrombocytopenia, anemia, and leukopenia appeared to diminish in incidence over the first four cycles of decitabine treatment; however, these toxicities remained frequent, most likely owing to the continuing presence of underlying disease and myelosuppression.

Decitabine has also been studied in MDS patients with disease recurrence who had previously responded to the drug. Rüter and colleagues reported recently on 22 patients who received decitabine retreatment at the time of disease relapse (Lubbert et al 2004; Ruter et al 2006). These patients had initially received a median of six courses of decitabine (range 2–6 courses), which resulted in a CR in 55% (12 of 22 patients), a PR in 27% (6 of 22), and a hematologic improvement in 18% (4 of 22). Decitabine retreatment was initiated at a median of 11 months after the last course of initial treatment. In the retreatment stage, patients received a median of three courses, resulting in 45% (10 of 22 patients) of patients responding (7 HI, 2 PR, and 1 CR). The median duration of second response was 4 months. Because the

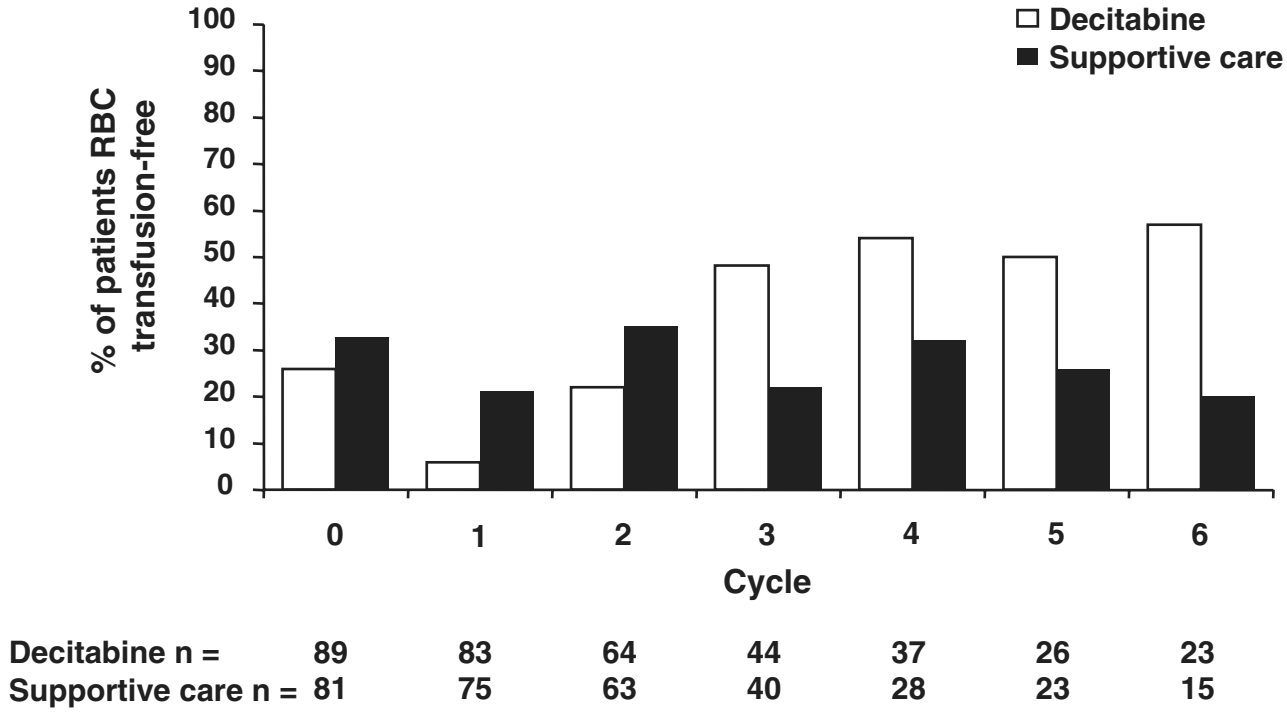

Figure 3 Percentage of patients red blood cell (RBC) transfusion free per cycle (Reprinted, with permission, from Kantarjian et al 2006).

quality and duration of the second response were inferior to those of the first response, the authors suggest that decitabine responders may derive more clinical benefit from a longer period of initial treatment.

Optimal dosing of decitabine

As previously described, decitabine is believed to have a dual mechanism of action depending on dose, with higher doses associated with cytotoxicity and lower doses associated with demethylation. Because of this dose-dependent mechanism of action, lower-dose schedules of decitabine may be safer and more effective than higher dose schedules. Indeed, early studies of decitabine using high doses of the drug showed activity in various types of hematologic malignancies but with significant prolonged myelosuppression (Santini et al 2001). In a more recent study, decitabine appeared significantly more active at lower doses compared with higher doses (Issa et al 2004).

In order to further optimize therapy with decitabine, Kantarjian and colleagues performed a randomized study of three low-dose schedules in patients with MDS and chronic myelomonocytic leukemia (CMML) (O'Brien et al 2005; Kantarjian et al 2005; Kantarjian et al 2007). The decitabine dose per course was reduced from the FDA approved dose of 135 mg/m^2 to 100 mg/m^2. In addition, the doses of decitabine were delivered every 4 weeks (rather than every 6–8 weeks), as long as there was persistent disease and no significant myelosuppression-associated complications, and therapy was continued for at least three courses before response was evaluated. The three dosing schedules were as follows: 20 mg/m^2 intravenously (IV) over 1 hour daily for 5 days (arm A), 10 mg/m^2 IV over 1 hour daily for 10 days (arm B), and 10 mg/m^2 subcutaneously (SQ) given twice daily for 5 days (arm C).

The results of the study by Kantarjian and colleagues indicate that lower dose schedules of decitabine have higher efficacy in MDS patients (O'Brien et al 2005; Kantarjian et al 2005; Kantarjian et al 2007). At least one course of therapy was received by 95 patients. Response criteria for CR and PR were the same as for AML (PR also requiring a decrease in blasts by >50%) but required response durability for at least 4 weeks. In total, 32 patients had a CR (34%), 1 patient had a PR (1%), 23 patients (24%) had marrow CR without (n = 10, 11%) or with other HI responses (n = 13, 14%), and 13 patients had an HI (14%). When analyzed by schedule, the complete response rates were 39% for arm A,

Table 3 Most common adverse events of decitabine

	Decitabine % (n = 83)*	Supportive care % (n = 81)
Neutropenia	90	72
Thrombocytopenia	89	79
Anemia NOS	82	74
Pyrexia	53	28
Nausea	42	16
Cough	40	31
Petechiae	39	16
Constipation	35	14
Diarrhea NOS	34	16
Hyperglycemia NOS	33	20
Febrile neutropenia	29	6
Leukopenia NOS	28	14
Headache	28	14
Insomnia	28	14
Edema, peripheral	25	16
Vomiting NOS	25	9
Hypoalbuminemia	24	17
Hypomagnesemia	24	7
Pallor	23	12
Pneumonia NOS	22	14
Rigors	22	17
Ecchymosis	22	15
Hypokalemia	22	12
Arthralgia	20	10

*Adverse events reported in ≥20% of patients in the decitabine group and at a rate greater than supportive care in the phase 3 myelodysplastic syndromes trial. NOS, not otherwise specified.

24% for arm B, and 21% for arm C (Table 4). The median number of courses to reach CR for all treatment groups was three (range, 1–7). Myelosuppression was the primary toxicity reported and it occurred more with arm B (Table 4). In summary, the schedule of 20 mg/m^2 IV over 1 hour daily for 5 days was found to be superior to the other two regimens and to offer an excellent therapeutic option in addition to the FDA approved dose (Table 5).

Approved indications for decitabine

Decitabine is approved for the treatment of patients with MDS, including previously treated or untreated, de novo or secondary MDS of all FAB subtypes (RA, RARS, RAEB, RAEB-T, and CMMoL) and intermediate-1, intermediate-2, and high-risk IPSS groups (Dacogen [package insert] 2006). Decitabine dosing for MDS is 15 mg/m^2 via a 3-hour continuous infusion three times a day for 3 days for the first treatment cycle, repeated every 6 weeks. It is recommended that patients be treated for a minimum of four cycles; however, it is noted that a complete or partial response may take longer than four cycles. Treatment may be continued as long as the patient continues to benefit. Patients may be premedicated with standard antiemetic therapy.

Decitabine treatment is associated with myelosuppression, so complete blood counts are recommended before each cycle of therapy, or as needed to assess toxicity (Dacogen 2006). After the first cycle of therapy, dose adjustments and delays may be required and are outlined in the package labeling. Clinicians should consider the early administration of growth factors and/or antimicrobial agents for prevention or treatment of infections. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles, and may not necessarily indicate progression of underlying MDS. Decitabine is contraindicated in patients with a known hypersensitivity to decitabine and carries a pregnancy category D rating.

Preparation and stability

Decitabine should be aseptically reconstituted with 10 mL of Sterile Water for Injection (USP) (Dacogen 2006). Immediately after reconstitution, the solution should be further diluted with 0.9% sodium chloride injection, 5% dextrose injection, or lactated Ringer's injection to a final drug concentration of 0.1–1.0 mg/mL. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2 °C–8 °C) infusion fluids and stored at 2 °C–8 °C (36 °F–46 °F) for up to a maximum of 7 hours until administration.

Azacitidine

Azacitidine is the only other approved hypomethylating agent for the treatment of MDS. Although similar in structure to decitabine, azacitidine contains ribose rather than deoxribose and is incorporated primarily into RNA and to a much lesser extent into DNA. This difference may account for the approximately 10-fold higher potency of decitabine compared with azacitidine (Creusot et al 1982).

In a randomized phase 3 trial of azacitidine in patients with MDS, azacitidine produced results similar to decitabine, with an ORR (CR + PR) in the azacitidine arm of 16.2% compared to 0% in the supportive care arm ($p < 0.0001$) (Silverman et al 2002; Kaminskas et al 2005). The CR rate in patients treated with azacitidine was 6.1% compared with 0% for patients treated with supportive care. Median time to AML or death was significantly increased with azacitidine treatment (21 months compared with 13 months for supportive care). As expected for this class of agent, the most common treatment-related toxicity was myelosuppression.

Because of the lack of any head-to-head trials, it is difficult to compare the efficacy of decitabine and azacitidine. Differences in study design between the two completed phase

Table 4 Efficacy and side effects of three alternative decitabine dosing schedules (Adapted, with permission, from Kantarjian et al (2007))

Parameter	Arm A (5-Day IV)	Arm B (10-Day IV)	Arm C (5-Day SQ)
No. patients	64	17	14
No. CR/treated (%)	25(39)	4(24)	3(21)
Median number of courses (range)	5(1–18)	9(1–15)	8(1–17)
Median duration of therapy in mos (range)	5.4(1.0–20.4+)	10.8(1.9–17.7+)	9.7(0.5–22.9+)
Median follow-up time (mos)	6.5	15	15
No. (%) still on therapy	39(61)	6(35)	3(21)
Median days to granulocytes recovery to 10^9/L or above	24	27	14
Median days to platelet recovery to 50 × 10^9/L or above	20	27	31
Median days to delivery of subsequent courses (range)	35	40	35
No. courses requiring hospitalization (%)	50(12)	23(23)	14(14)

Abbreviation: IV, intravenous; SQ, subcutaneous; CR, complete response.

3 trials add to this difficulty. Patients in the phase 3 azacitidine study were able to stay on treatment longer, resulting in a median of nine treatment cycles (Silverman et al 2002), compared with those in the phase 3 decitabine trial who received a median of three treatment cycles (Kantarjian et al 2006). The median duration of MDS was 7.3 months in the decitabine study compared with 2.8 months in the azacitidine trial, suggesting that the decitabine patients had more aggressive disease (Silverman et al 2002; Kantarjian et al 2006). In addition, response criteria in the azacitidine trial were less rigorous, requiring a CR or PR for at least 4 weeks and not requiring disappearance of dysplastic changes (Silverman et al 2002), compared with the decitabine study in which response was determined using IWG criteria (Kantarjian et al 2006).

Future considerations

Clinical studies are now under way to evaluate combination therapy with decitabine and other agents. Farthest along in development is the combination of decitabine and histone deacetylase (HDAC) inhibitors such as valproic acid. Results from a recent phase 1/2 study of decitabine and valproic acid suggest that this combination has significant activity in patients with AML and MDS and is associated with changes in histone acetylation and DNA hypomethylation (Garcia-Manero et al 2006). Other agents that are being studied in combination with decitabine include amsacrine, idarubicin, daunorubicin, topotecan, cisplatin, carboplatin, and imatinib (Plumb et al 2000; Garcia-Manero and Gore 2005).

Table 5 Decitabine dosing schedules

Dacogen regimen	IV Dose and schedule	Total dose/course
FDA approved*	15 mg/m^2 over 3 hours every 8 hours × 3 days every 6 weeks	135 mg/m^2
Active alternative†	20 mg/m^2 over 1 hour daily × 5 days every 4 weeks	100 mg/m^2

*Kantarjian et al (2006);
†Kantarjian et al (2007)

Decitabine therapy, alone and in combination with other agents, has shown encouraging results in other studies involving AML patients (Rivard et al 1981; Momparler et al 1985; Pinto et al 1989; Petti et al 1993; Lubbert et al 2005). Preliminary results from a recent phase 2 study in AML patients not eligible for induction chemotherapy suggest that decitabine is an active first-line treatment (Lubbert et al 2005). Decitabine was administered at a dose of 135 mg/m^2 IV over 72 hours repeated every 6 weeks for up to four courses, with all-transretinoic acid (ATRA) administered at a dose of 45 mg/m^2 per day for 28 days during the second course in decitabine-sensitive patients. In the 29 fully evaluable patients, a CR was observed in four patients (14%) and a PR was observed in five patients (17%). Toxicities with decitabine were similar to those described for MDS, and no unexpected toxicities were observed with the combination of decitabine plus ATRA.

Although not within the scope of this review, decitabine is also being evaluated in chronic myelogenous leukemia (CML) (Sacchi et al 1999; Kantarjian et al 2003; Issa et al 2005) and in some solid tumors including renal, ovarian, colorectal, and cervical cancer (van Groeningen et al 1986; Abele et al 1987; Sessa et al 1990; Clavel et al 1992; Momparler et al 1997; Thibault et al 1998; Schwartsmann et al 2000; Plumb et al 2000; Samlowski et al 2005; Stewart et al 2005; Gollob et al 2006).

Summary

Results from phase 2 and phase 3 studies indicate that decitabine is effective in the treatment of MDS, resulting

in durable clinical responses and delayed time to AML transformation or death.

Decitabine has been shown to be well tolerated, with a toxicity profile expected for this class of agents. Recent studies suggest that the efficacy of decitabine may be further optimized by allowing for multiple treatment cycles and by using lower-dose schedules such as a schedule of 20 mg/m^2 IV over 1 hour daily for 5 days. Future directions for decitabine include its use in combination therapy with agents such as HDAC inhibitors and in AML.

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