Decitabine Can Be Safely Reduced After Achievement of Best Objective Response in Patients With Myelodysplastic Syndrome

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Abstract

Effects of dose delay and dose reduction (DD/DR) on outcomes of patients with myelodysplastic syndrome (MDS) treated with decitabine are unknown. We analyzed patients with MDS treated with decitabine on 3 different schedules. We found that patients who had DD/DR before achieving best objective response had worse outcomes compared with DD/DR after best objective response. We conclude that DD/DR of decitabine is feasible. However, adhering to a decitabine schedule is important to achieve best outcome, especially before obtaining the best objective response.

Background: Decitabine is standard therapy in patients with myelodysplastic syndrome (MDS). Current recommendations suggest a dose of 20 mg/m^2 intravenously (IV) daily for 5 days every 4 weeks. However, this therapy is associated with frequent grade 3/4 hematologic toxicity, requiring dose delays and/or dose reductions (DD/DR). **Results:** We investigated the outcomes of 122 patients with MDS who had DD/DR of frontline decitabine therapy. Sixty-five patients (53%) had DR by at least 25% or DD (defined as a delay beyond 5 weeks between cycles). Thirty-five patients (29%) underwent DD/DR after achieving best objective response, 30 patients (25%) underwent DD/DR before best objective response, and 57 (54%) patients had no DD/DR. There was a trend for more durable responses in favor of patients requiring DD/DR after the achievement of best objective response (median not reached) ($P = .161$). Overall survival rates were significantly higher for patients who had DD/DR after best objective response compared with those who had DD/DR before best objective response or those with no DD/DR (30 vs. 22 vs. 11 months, respectively; $P < .001$). Progression-free survival (PFS) rates also trended higher for those with DD/DR after best objective response (median not reached) compared with those who required DD/DR before best objective response (median of 15 months) ($P = .285$). **Conclusion:** DD/DR may be safely accomplished once the patient has achieved best objective response (preferably complete remission [CR]) without impacting outcome. Prospective evaluation of an approach conceived of a loading dose for induction of a best objective response followed by a maintenance schedule is to be considered.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. S2, S289-94
Keywords: Decitabine, Dose delay, Dose reduction, Myelodysplastic syndrome

Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of hematologic disorders characterized by clonal expansion of a hematopoietic progenitor cell, leading to bone marrow dysfunction, pancytopenia, and a tendency to convert to acute leukemia.[1,2] Methylation plays an important role in the development of these diseases, and hypermethylation can lead to silencing of important tumor suppressor genes and is thought to contribute to MDS pathophysiology.[3] Decitabine is a hypomethylating agent (HMA) that has been shown to improve outcomes of patients with MDS.[4-6]

Decitabine is standard therapy in patients with MDS. Current recommendations suggest a dose of 20 mg/m^2 intravenously (IV) daily for 5 days every 4 weeks. However, this therapy is associated

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Submitted: May 8, 2013; Accepted: May 8, 2013; Epub: Aug 19, 2013

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2013.05.025

with frequent grade 3/4 hematologic toxicity, requiring dose delay and/or dose reduction (DD/DR).[7] Patients with MDS frequently present with myelosuppression as a result of their disease. This leads to frequent DD/DR during decitabine treatment. In a phase II study assessing the decitabine regimen of 20 mg/m^2 IV daily for 5 days, grade 3 or higher neutropenia, thrombocytopenia, febrile neutropenia, and anemia occurred at rates of 31%, 18%, 14%, and 12% of patients, respectively.[8] Thirty-two percent of the administered cycles in that study were delayed primarily because of myelosuppression. Most of these delays occurred during the first cycles of treatment. The effect of DD/DR on response to treatments and patient outcomes are unknown. The aim of this study is to assess the impact of the timing and occurrence of DD/DR of decitabine on the outcome of patients with MDS treated with decitabine at our institution.

Patients and Methods

Study Group

One hundred twenty-four patients with MDS treated between November 2003 and July 2010 with frontline decitabine were retrospectively analyzed for DD/DR. Informed consent was obtained according to institutional guidelines and in accordance with the Declaration of Helsinki.[6] The study was fully approved by The University of Texas MD Anderson Cancer Center Surveillance Committee. The French-American-British morphologic classification was used for MDS and chronic myelomonocytic leukemia (CMML) diagnosis. Eligibility criteria included (1) age 16 years or older, (2) diagnosis of MDS with intermediate- or high-risk International Prognostic Scoring System (IPSS) scores, or diagnosis of CMML,[9] and normal organ function.[10,11] Patients who had undergone previous intensive chemotherapy with cytarabine 1 g/m^2 or more were not eligible. Diagnosis of CMML was based on the typical morphologic picture: unexplained leukocytosis greater than 12 $\times$ 10^9/L lasting for at least 3 months, exclusion of other myeloproliferative disorders, and presence of at least 1 $\times$ 10^9/L monocytes.[11]

Therapy

Patients were randomized to receive decitabine on 1 of 3 schedules: (1) 20 mg/m^2 IV[12] over 1 hour daily for 5 days (n = 93), (2) 20 mg/m^2 daily for 5 days given in 2 subcutaneous (SC) doses daily for 5 days (n = 14),[9] or 10 mg/m^2 IV over 1 hour daily for 10 days (n = 17).[6] All patients received the same decitabine total dose per course—100 mg/m^2. Courses of decitabine were given every 4 weeks (at least in the first 3 courses) regardless of the counts as long as (1) there were no significant myelosuppressive life-threatening complications with a particular course, (such as pneumonia, severe infection, or bleeding) or severe organ damage and (2) there was evidence of persistent disease. No dose escalations were considered. Dose reductions by 25% to 30%, rounded to 15, 10, 7.5, and 5 mg/m^2, were allowed for grade 3 or 4 nonmyelosuppressive toxicities, for severe myelosuppression-associated complications (infections, bleeding), or for prolonged myelosuppression defined as a hypocellular marrow (5% or less cellularity) without evidence of disease for 6 weeks or more after the start of a course of therapy. Other dose modifications (eg, 50% DRs) were occasionally considered for severe complications if judged to be in the best safety interest of the patient. Use of erythropoietin and granulocyte-colony stimulating factor (G-CSF) was allowed as indicated by the clinical condition. In general, erythropoietin at a dose of 40,000 units SC weekly was allowed for red cell transfusion dependence or for a hemoglobin level $<$ 10 g/dL. G-CSF 300 to 480 μg SC was given if the granulocyte count was $<$ 1 $\times$ 10^9/L in the setting of a febrile episode or documented infection or in a patient in complete remission (CR) but with granulocyte counts $<$ 1 $\times$ 10^9/L before initiation of the next course of decitabine.

Response Criteria and Statistical Considerations

Response criteria for CR and partial remission were identical to the ones used for acute myeloid leukemia but required response durability for at least 4 weeks.[6] CR required normalization of the bone marrow and peripheral counts with $\leq$ 5% marrow blasts, a granulocyte count of $\geq$ 1 $\times$ 10^9/L, and a platelet count of $\geq$ 100 $\times$ 10^9/L, lasting for at least 4 weeks. A partial remission was similar to CR except for persistent marrow blasts $>$ 5%, but which were reduced by $\geq$ 50%. A marrow CR (mCR) referred to reduction of marrow blasts to $\leq$ 5% without normalization of peripheral counts. Response duration was dated from first evidence of response until disease progression.[10] DD was defined as a delay beyond 5 weeks between cycles. Best objective response was determined by International Work Group modified response criteria. Survival data were reported from the start of therapy and were obtained by Kaplan-Meier survival curves. Overall survival (OS) was defined as the time from the start of therapy until death. Progression-free survival (PFS) was defined as the time from the start of therapy until progression of MDS or transformation to acute myeloid leukemia (increased blasts to $\geq$ 30% in the blood and/or the bone marrow). The curves were compared using the log-rank test.

Results

Patient Characteristics

A total of 124 patients were assessed. For the purpose of this analysis, patients were divided into 3 groups: patients who had no DD/DR, those who had best objective response before DD/DR, and those who had best objective response after DD/DR. Median age at diagnosis was 65 years (range, 37-90 years). Eastern Cooperative Oncology Group performance status was 0 or 1 in 98% of the patients. Patients who had best objective response after DD/DR were more likely to have higher baseline hemoglobin values (P = .01), and the number of decitabine cycles was significantly higher for patients who had best objective response before DD/DR (P $<$ .001). There were no other statistically significant differences in characteristics between the 3 groups of patients. Baseline characteristics are summarized in Table 1.

Response to Treatment

Response to decitabine treatment is summarized in Table 2. Overall, 74 (60%) patients responded, with 53 (43%) achieving a CR, 5 (4%) mCR, and 16 (13%) clinical benefit (CB). We then analyzed responses to treatment vis-a-vis the timing of DD/DR (Table 2). Sixty-five patients (53%) had DR of $\geq$ 25% or DD for a median of 7 days (range, 1-97 days). Thirty-five patients (28%) achieved best objective response before DD/DR. In the other