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Decitabine in patients with newly diagnosed and relapsed acute myeloid leukemia

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Abstract

Treatment options for older patients with acute myeloid leukemia (AML) and for patients with relapsed/refractory AML are limited, and outcomes are poor. Decitabine, a hypomethylating agent, is active in patients with myelodysplastic syndrome (MDS) and AML, but its optimal dose and schedule are unknown. We report the efficacy and safety of repeated 10-day cycles of decitabine 20 mg/m^2 administered intravenously over 1 h in 52 newly diagnosed and 102 relapsed/refractory patients. Repeated 10-day cycles of decitabine produced a complete response (CR) in 40% of newly diagnosed older patients with AML, many of whom had adverse prognostic features. The median overall survival (OS) was 318 days but there was prolonged survival in responders of 481 days. Relapsed/refractory patients had a CR rate of 15.7% with a median OS of 177 days. Extramedullary toxicity was mild and the regimen was well tolerated for ongoing post-remission, outpatient maintenance cycles. Responses were durable for over 1 year.

Keywords

Leukemia; myeloid; acute; drug therapy; treatment outcome; induction chemotherapy/methods

Introduction

Treatment options for older patients with acute myeloid leukemia (AML) and for relapsed/refractory patients of any age with AML are limited, and outcomes are generally poor. These patients are often ineligible for intensive anti-leukemic therapy or clinical trial participation due to poor performance status and/or inadequate organ function. Among untreated patients over age 60 years with a good performance status, 40–50% can achieve a complete response, but cure rates are < 10% and median overall survival is under 1 year [1,2]. For older patients with adverse prognostic features, such as poor performance status, unfavorable cytogenetics or an antecedent hematologic disorder, expected rates of complete response (CR) are < 20%, early mortality can be as high as 50% and 1-year survival is < 10% [3,4]. For patients whose first CR is < 1 year, the probability of obtaining a second CR

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is 10–20% [5] Furthermore, even for younger patients able to undergo intensive chemotherapy salvage, the overall survival is < 40% at 2 years [6].

Decitabine (5-aza-2'-deoxycytidine; Dacogen) was approved by the United States Food and Drug Administration for the treatment of myelodysplastic syndrome (MDS) on the basis of its ability to improve hematologic and quality of life parameters. It is generally well tolerated, with a favorable extramedullary toxicity profile and infrequent treatment-related mortality. Decitabine is activated intracellularly by deoxycytidine kinase and other nucleotide kinases to the active metabolite 5-aza-2'-deoxycytidine-triphosphate (5-aza-2'-dCTP), which can be incorporated into DNA during the S-phase of the cell cycle. Decitabine is believed to exert its antineoplastic effects by inhibition of DNA methyltransferases, causing DNA hypomethylation and activation of genes involved in differentiation and apoptosis. Although early studies established the safety and efficacy of decitabine at doses up to 3000 mg/m^2, more recent work has focused on lower total doses (100–200 mg/m^2) sufficient to induce DNA hypomethylation and myeloid differentiation.

Decitabine demonstrated single-agent efficacy in a phase II multicenter study of older patients with AML, with a CR rate of 25%, 30-day mortality of 7%, median overall survival 7.7 months and little extramedullary toxicity when administered using a schedule of 20 mg/m^2 over 1 h daily for 5 days [7]. Patients received a median of three cycles of treatment, with a range of 1–25 cycles. Decitabine administered in the same dose and schedule was shown to have a modest survival benefit over low-dose cytarabine and supportive care (7.7 months decitabine vs. 5.0 months, hazard ratio [HR] = 0.82, $p = 0.037$) in a randomized trial of 485 newly diagnosed older patients with AML [8].

Blum *et al*. treated 53 newly diagnosed patients with AML (median 74 years, range 60–85) with decitabine 20 mg/m^2 daily for 10 days every 4 weeks, with 47% CR after a median of 3 cycles [9]. Induction mortality was 2% within 30 days and 15% within 8 weeks, mostly due to disease progression. Median overall and disease-free survivals were 55 and 46 weeks, respectively. Unlike with low-dose cytarabine, patients with unfavorable features, including complex cytogenetic abnormalities and baseline hyperleukocytosis, achieved a CR.

The objective of this study was to review the treatment outcomes of newly diagnosed older patients with AML and patients with relapsed AML aged ≥ 18 years treated with decitabine at Weill Cornell Medical Center/The New York Presbyterian Hospital. Many were ineligible for standard chemotherapy or investigational trials due to organ dysfunction, performance status or ongoing infection.

Materials and methods

Permission was granted by the Institutional Review Board of Weill Cornell Medical College to review the charts of all patients with AML treated with decitabine at the institution starting in 2007. AML was defined using the World Health Organization criteria, with ≥ 20% myeloblasts [10]. The study population included 52 patients (age 59–90 years) with newly diagnosed, untreated AML (cohort 1) and 102 patients with relapsed/refractory AML (cohort 2). Newly diagnosed patients were treated with decitabine 20 mg/m^2 intravenously over 1 h for repeated 10-day cycles approximately every 28 days until CR. After CR, most of the patients were treated with ongoing 5-day cycles of decitabine at 20 mg/m^2 until toxicity or progression of disease. In the relapsed/refractory group, 45 patients received repeated 5-day cycles of decitabine 20 mg/m^2 daily combined with one dose of gemtuzumab ozogamicin (GO) 3 mg/m^2 on day 5. Fifty-seven of the relapsed/refractory patients were treated with ongoing 10-day cycles of decitabine 20 mg/m^2. Treatment cycles were repeated if there was stable disease or evidence of clinical, hematologic and/or marrow response. The

treatment intervals varied depending on clinical circumstances, but were mostly between 28 and 42 days. Patients receiving 10-day cycles of decitabine who had stable disease, hematologic improvement or CR were treated with ongoing cycles of decitabine 20 mg/m^2 for 3–5 days every 4–6 weeks as tolerated until progression. Bone marrow biopsies were performed at the discretion of the treating physician and assessed as per Cheson *et al*. [11] Adverse events were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 3.0.

All patients were treated in the specialized inpatient and outpatient facilities of the Weill Cornell Medical Center/New York Presbyterian Hospital and were attended by the same group of physicians, nurses and support staff. Clinical care was administered as per the standard algorithms of the Weill Cornell Leukemia Program, including antibiotic and antifungal prophylaxis, treatment of neutropenia-related infections, use of hematopoietic growth factors and transfusion support for anemia and thrombocytopenia.

Statistical analysis

Descriptive statistics (including mean, standard deviation, median, range, frequency, percent) were calculated to characterize the two study cohorts. The primary endpoint of the study was overall survival (OS). Secondary endpoints included CR, complete response with incomplete platelet recovery (CRi) and duration of CR. Overall survival (defined as the interval between the date of initial treatment and the date of last follow-up or death) was estimated by Kaplan–Meier survival analysis. Univariate associations between demographic/clinical variables and overall survival were assessed by the log-rank test. The independent effect of demographic/clinical predictors on overall survival was assessed by multivariate Cox proportional hazards regression analysis. All of the above analyses were performed separately for untreated patients with AML (cohort 1) and patients with relapsed/refractory AML (cohort 2). Adjusted hazard ratios were computed and 95% confidence intervals (CIs) for the hazard ratios and median overall survival time estimates are presented to assess the precision of the obtained estimates. Median follow-up time for each cohort of patients was computed based on survivors. All *p*-values are two-sided, with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in SPSS Version 19.0 (SPSS, Inc., Chicago, IL) and Stata Version 12.0 (StataCorp, College Station, TX).

Role of the funding source

Sources of funding had no role in the design, collection, analysis or interpretation of the data.

Results

Cohort 1: newly diagnosed AML

The characteristics of the 52 newly diagnosed patients treated with decitabine are described in Table I. The median age was 75 years (range 45–91 years), with 23 males (44.2%) and 29 females (55.8%). Two patients under 60 years with poor performance status and multiple medical comorbidities were included. The majority of patients were older than 70 years and 13 patients were ≥ 80 years. Most patients (80.8%) had Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 1, with 18 (34.6%) ≥ ECOG 2. Cytogenetics were classified using criteria of the Cancer and Leukemia Group B (CALGB), and were adverse in 18 patients (34.6%) and intermediate in 34 patients (65.4%) [12]. No patient had favorable cytogenetics. Twenty-seven patients (51.9%) had secondary AML or an antecedent MDS or myeloproliferative disorder. Molecular diagnostics were available for 25 patients, with mutations of *FLT3-ITD* in six (24.0%), *NPM1* in eight (32.0%) patients and

JAK-2 in four (16.0%). Five patients (9.6%) had baseline bilirubin > 1.5 × upper limit of normal and four (7.7%) had baseline creatinine > 2 mg/dL, which are common eligibility restrictions for clinical trials. Median baseline white blood cell count (WBC) was $5 \times 10^3/\mu L$ (range 0.6–186.3 × $10^3/\mu L$), with 10 patients (19.2%) > 20 × $10^3/\mu L$.

Among the 52 newly diagnosed patients with AML (cohort 1), 21 achieved a CR, for a total response rate of 40.4% (Table II). One patient with presumed CR had normal peripheral blood counts after treatment, but refused confirmatory bone marrow biopsy. CR was achieved in 6/18 (33.3%) patients with adverse cytogenetics, in two patients with baseline WBC > 15 × $10^3/\mu L$ and in one patient with baseline WBC > 100 × $10^3/\mu L$. Both patients under 60 years who started treatment with multi-organ dysfunction achieved a CR, and the oldest patient with a CR was 85 years. None of the six patients who had previously been treated with azacitidine or decitabine for MDS achieved a CR. If these patients are excluded from the study population, the CR rate is 46%. The median overall survival was 318.0 days (95% CI = 275.0–361.0 days), with 30- and 60-day mortality 5.8% and 15.4%, respectively. Among the responders, one patient (age 45) went on to allogeneic stem cell transplant and remains in CR. Not surprisingly, overall survival was significantly longer among responders, with median overall survival 481.0 vs. 206.0 days in non-responders, $p = 0.002$. CR remained a significant predictor of improved overall survival in multivariate Cox regression analysis (adjusted HR = 0.38; 95% CI = 0.20–0.75; $p = 0.005$). Baseline WBC < 10 × $10^3/\mu L$ vs. ≥ 10 × $10^3/\mu L$ (median OS = 335.0 vs. 199.0 days, respectively, $p = 0.14$) and ECOG 0–1 vs. 2–4 (median OS = 375.0 vs. 94.0 days, respectively, $p = 0.15$) demonstrated trends for improved overall survival, but did not reach statistical significance. ECOG status of 0 or 1 (adjusted HR = 0.67; 95% CI = 0.35–1.28; $p = 0.22$) and baseline WBC < 10 × $10^3/\mu L$ (adjusted HR = 0.71; 95% CI = 0.38–1.34; $p = 0.29$) also demonstrated statistically non-significant trends toward improved overall survival on multivariate analysis.

All patients in cohort 1 received at least one 10-day induction cycle with decitabine 20 mg/m^2. The median number of treatment cycles was 2 (range 1–18). Patients required a median number of 2 cycles (range 1–4) to achieve a response, with a median time to CR of 55.5 days (range 18.0–122.0 days). The median time to neutrophil recovery was 42.5 days (range 20.0–120.0 days), and the median time to platelet count recovery was 48.0 days (range 0.0–130.0 days). Among the 20 responding patients who had evaluable bone marrow pathology, only five (25.0%) had a hypocellular marrow after the first cycle of decitabine, and two of these five patients had increased blasts noted within the hypocellular marrow. The other 15 responders all had normocellular or hypercellular marrows with increased blasts after the first cycle of decitabine.

Myelosuppression was noted in all patients. Extramedullary toxicity was generally mild, with no events of grade 3 or higher hepatic or renal dysfunction. Twenty-nine patients (55.8%) had neutropenic fever with bacteremia requiring IV antibiotics. The most frequent infections were with *Escherichia coli*, *Enterococcus faecium*, *Staphylococcus* species and *Pseudomonas*. One patient developed disseminated candidiasis. Patients were hospitalized for a median of 39 days (range 0–169 days). However, it should be noted that the reasons for prolonged hospitalization were frequently social or logistical, rather than medical.

Cohort 2: relapsed/refractory AML

The characteristics of the 102 patients with relapsed/refractory AML who received salvage therapy with decitabine are summarized in Table III. There were 53 males (52.0%) and 49 females (48.0%) ranging in age from 21 to 88 years (median 66 years). The median number of prior treatments was 2 (range 1–5). Twenty-five patients were ECOG 0 (24.5%), 50 were ECOG 1 (49.0%), 19 ECOG 2 (18.6%), seven ECOG 3 (6.9%) and one was unknown.

Seventy-one patients (69.6%) had intermediate-risk cytogenetics and 31 (30.4%) had adverse risk cytogenetics. No patient had favorable risk cytogenetics. Five patients (4.9%) were known to have mutations in *FLT3-ITD* and three (2.9%) in *NPM1*. Fifty-eight patients (56.9%) received decitabine-based salvage after standard anthracycline-based chemotherapy with 3 + 7. Forty patients (39.2%) were treated with decitabine-based salvage after a low-intensity induction, such as low-dose cytarabine (Ara-C), lenalidomide, arsenic trioxide combined with low-dose Ara-C or 5-azacitadine. Sixty patients (58.8%) received single-agent decitabine and 42 (41.2%) received decitabine combined with gemtuzumab ozogamicin; there were no significant differences between these groups with respect to age, performance status, cytogenetics or presenting WBC. Five patients (4.9%) were treated with decitabine for relapse after allogeneic transplant. Eight patients (7.8%) had baseline bilirubin > 1.3 and 19 patients (18.6%) had baseline creatinine > 1.3 mg/dL.

Sixteen patients achieved a CR, for an overall response rate of 15.7%. Complete responses were seen regardless of the number of prior therapies. The median overall survival was 177.0 days (95% CI = 148.0–206.0 days). Responding patients received up to 28 cycles of treatment. One chemotherapy-refractory patient who achieved CR with decitabine subsequently underwent allogeneic stem cell transplant and remains in remission more than 3 years later.

Univariate analysis identified achievement of CR vs. no response (NR) (median OS = 455.0 vs. 169.0 days, respectively, $p < 0.0001$) and ECOG 0–1 vs. 2–4 (median OS = 207.0 vs. 160.0 days, respectively, $p = 0.02$) as significant predictors of improved overall survival. Treatment with single-agent decitabine vs. decitabine combined with gemtuzumab ozogamicin (median OS = 209.0 vs. 107.0 days, respectively, $p = 0.13$) demonstrated a non-significant trend for improved overall survival. In multivariate Cox regression analysis, achievement of CR (adjusted HR = 0.34; 95% CI = 0.18–0.62; $p < 0.0001$) and ECOG status of 0 or 1 (adjusted HR = 0.58; 95% CI = 0.37–0.92; $p = 0.02$) remained significant predictors of improved overall survival; age, cytogenetics, presenting WBC, hepatic and renal function, and number of prior regimens were not significant predictors. Treatment with single-agent decitabine (adjusted HR = 0.70; 95% CI = 0.46–1.05; $p = 0.08$) demonstrated a non-significant trend for improved overall survival on multivariate analysis.

Discussion

This study presents a large, retrospective, single-institution experience using decitabine in newly diagnosed older patients and relapsed/refractory adults of all ages with AML. Decitabine demonstrated activity and acceptable toxicity in both groups, with a CR rate of 40.4% in the former and 15.7% in the latter. Given the widespread use of hypomethylating agents (HMAs) in MDS, it is of interest to note that none of our newly diagnosed patients with prior HMA exposure achieved a CR. It is important to further investigate whether prior HMA exposure for MDS definitively precludes response to the same or other HMAs if the disease progresses to AML. While the single-agent response rate in relapsed AML is not compelling and the addition of gemtuzumab did not seem to offer much benefit, the safety profile suggests that decitabine could be combined with other agents or increased to a 10-day schedule in combination with gemtuzumab. The data for newly diagnosed older patients are more encouraging and prompt several questions, including: (1) how do the outcomes with decitabine compare with those using other therapies, and (2) how can the use of this agent in AML be optimized in future clinical trials?

Although direct comparisons cannot be made, the responses using 10-day cycles of decitabine appear slightly better than our data from other low-intensity therapies over the last decade, including low-dose cytarabine, arsenic trioxide combined with cytarabine, and

tipifarnib combined with etoposide [13–15]. With respect to understanding the relative intensity of decitabine compared to other regimens, there are several important considerations for clinical care. First, the regimen, though generally well tolerated, is myelosuppressive, and patients require significant transfusion support and management of neutropenic infections. Second, results from bone marrow aspirations and biopsies taken at day 28 or sooner following the first cycle of decitabine are often misleading. Many patients, including those who eventually achieve remission, have a normocellular or hypercellular marrow with clear evidence of residual disease at these early time points. Ten-day cycles of decitabine should be repeated approximately every 28 days until CR and interrupted only in the events of grade 3 or higher extramedullary toxicity or severely hypocellular bone marrow aspirate/biopsy. Finally, it should be noted that in both the Ohio State and Cornell experiences, patients in CR received ongoing monthly 5-day maintenance cycles of decitabine until the time of disease progression or toxicity. Although the necessity of these ongoing cycles has not been definitively demonstrated, they are well tolerated in the out-patient setting and, for now, should be viewed as required to achieve the predicted outcomes.

Efforts are under way to identify subgroups of patients who may specifically benefit from treatment with decitabine. Ravandi *et al*. have shown that treatment with hypomethylating agents may be superior to standard chemotherapy in patients with monosomies 5 and 7 [16]. Lubbert *et al*. have also found encouraging results with decitabine in these unfavorable cytogenetic subtypes [17]. Blum *et al*. showed that responders to decitabine have higher pretreatment levels of microRNA (*miR*) 29b [9]. Disruption of the SP1/nuclear factor-κB (NF-κB) (p65) complex by the proteasome inhibitor bortezomib has been shown to inhibit growth of leukemic cells via up-regulation of *miR-29b*, and decitabine has been combined with bortezomib in a phase 1 clinical trial [18,19]. A randomized phase II clinical trial of decitabine versus decitabine combined with bortezomib is ongoing in the Alliance Cooperative Group [20]. This trial also includes comprehensive geriatric functional assessments and quality of life measurements, which are critical to evaluate treatment strategies for older patients. Comprehensive genomic profiling may also identify those older patients most likely to benefit from decitabine. Preliminary data suggest that *DNMT3* or *FLT3* mutations may be of particular interest.

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Table I

Baseline characteristics of newly diagnosed patients with AML (cohort 1).

Total number of patients	***n* = 52**
Median age (years, range)	75 (45–91)
Percent ≥ 80 years	25
M/F (%)	44/56
ECOG performance status (%)	
0	19
1	46
2	23
3	8
4	4
Cytogenetics (%)	
Adverse	35
Intermediate	65
Baseline WBC, $\times 10^9$/L (%)	
< 10	65
≥ 10	35
Baseline bilirubin (%)	
≤ 1.3	81
> 1.3	19
Baseline creatinine (%)	
≤ 1.3	81
> 1.3	19

AML, acute myeloid leukemia; M/F, male/female; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell count.

Table II

Newly diagnosed patients with AML (cohort 1): characteristics of responders versus non-responders.

	CR	NR
Total	21 (40.4%)	31 (59.6%)
Overall survival (days)	481	206
Median age, years (range)	74 (45–86)	77 (60–91)
Adverse cytogenetics (n = 18)	6 (33.3%)	12 (66.7%)
WBC > 15 × $10^3/\mu L$ (n = 10)	3 (30%)	7 (70%)
Prior HMA (n = 6)	0	6 (100%)

AML, acute myeloid leukemia; CR, complete response; NR, no response; WBC, white blood cell count; HMA, hypomethylating agent therapy, azacitidine or decitabine.

Table III

Characteristics of patients with relapsed/refractory AML (cohort 2).

Total number of patients	***n* = 102**
Median age (years, range)	66 (21–88)
M/F (%)	52/48
Median no. of prior therapies (range)	2 (1–5)
Prior anthracycline/ara-C induction (%)	57
Prior low-intensity induction (%)	39
Decitabine single-agent salvage (%)	59
Decitabine + GO salvage (%)	41
ECOG performance status (%)	
0	25
1	49
2	19
3	7
Unknown	1
Cytogenetics (%)	
Adverse	30
Intermediate	70
Baseline bilirubin (%)	
≤ 1.3	92
> 1.3	8
Baseline creatinine (%)	
≤ 1.3	81
> 1.3	19
CR	16 (15.7%)
NR	86 (84.3%)

AML, acute myeloid leukemia; M/F, male/female; GO, gemtuzumab ozogamicin; ECOG, Eastern Cooperative Oncology Group; CR, complete response; NR, no response.