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Second-line mitoxantrone, etoposide, and cytarabine for acute myeloid leukemia: A single-center experience

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The majority of patients with acute myeloid leukemia (AML) will require second-line chemotherapy for either relapsed or refractory disease. Currently, only allogeneic hematopoietic cell transplantation (HCT) offers a curative option in this setting and no preferred regimen has been established. The reported efficacy of second-line regimens is widely disparate, thus limiting informed clinical decision making. A retrospective review of 77 patients receiving therapy between 2001 and 2008 with relapsed, 42, and refractory, 35, AML was performed to determine overall response rate and survival following mitoxantrone (8 mg/m^2/day), etoposide (100 mg/m^2/day), and cytarabine (1,000 mg/m^2/day) chemotherapy administered over 5 days. Among 77 patients (median age of 54 years and 64% intermediate risk karyotype) with median follow-up of 153 days, 18% achieved a complete response and 8% a morphologic leukemia-free state. Fifty-seven (74%) experienced treatment failure, 10 of whom achieved a remission after additional therapy. Median overall survival (OS) was 6.8 months. Among patients achieving a response, 50% received consolidation with allogeneic HCT, autologous HCT (5%), or consolidation chemotherapy alone (45%). A nonsignificant trend in overall response (50%, 27%, and 23.8%) and median OS (8.3, 6.8, and 4.7 months) was observed by cytogenetic stratification into favorable, intermediate, and unfavorable risk. Patients with refractory versus relapsed disease had similar overall responses (20% and 31%, $P = 0.41$) and median OS (5.3 and 7.6 months, $P = 0.36$). Despite risk stratification by the European Prognostic Index, our series demonstrates inferior rates of response and survival, illustrating the limited activity of this regimen in our cohort. Am. J. Hematol. 85:877–881, 2010. © 2010 Wiley-Liss, Inc.

Introduction

Although intensive induction chemotherapy is effective in inducing a complete response (CR) in 50–80% of young (<60 years old) patients with acute myeloid leukemia (AML), the majority obtaining a CR eventually relapse and subsequently succumb to their disease [1–3]. Allogeneic hematopoietic cell transplantation (HCT) is generally accepted as the only curative approach for relapsed or refractory disease [4]. However, second-line HCT is limited by availability of an appropriately matched donor as well as transplant-related morbidity and mortality particularly among older or heavily pretreated patients.

Second-line chemotherapy regimens including mitoxantrone, etoposide, and cytarabine (MEC) have been commonly used to obtain disease control preceding HCT or as primary treatment for relapsed disease among patients not eligible for HCT [5]. When first introduced in 1991, the CR rate following second-line MEC was reported at 61–66% with 4–5-month median overall survival (OS) [5,6]. However, in two recent phase III randomized trials, the response rates in the placebo arm to a single cycle of second-line MEC were only 19 and 28%, although OS was similar to the earlier studies, 5.4 and 5.2 months [7,8]. Because of the differences in eras of practice including advances in diagnosis and treatment, isolating the patient-, disease-, or therapy-specific factors that contribute to these variable response rates remain challenging.

Currently, among a number of other regimes, MEC chemotherapy remains a backbone for the addition of novel agents in the relapsed or refractory setting [9]. Accordingly, the design of both placebo controlled and noncontrolled trials requires an accurate assessment of the baseline response rate to the chemotherapy regimen without the investigational agent. In this study, we reviewed the data of 77 patients with relapsed or refractory AML who received second-line MEC therapy after failure of first-line chemotherapy. The aims of this study were to analyze the efficacy and toxicity of MEC in the current era of diagnosis and supportive care at a tertiary care institution.

Methods

Patients. This retrospective study was approved by the Institutional Review Board of Stanford University's Research Compliance Office (Protocol no. 18329). Consecutive adult patients, receiving second-line MEC chemotherapy for relapsed or refractory AML between January 18, 2001 and April 22, 2008 and treated at Stanford University Medical Center were selected for review. Additional criteria for review were age 18 years or greater, diagnosis of AML excluding M3 according to the morphologic French-American-British (FAB) classification on the basis of bone marrow aspirate, and relapsed or refractory disease [10]. Refractory or resistant disease was defined by persistent AML in the peripheral blood or bone marrow (aspirate or biopsy) at least 7 days following prior chemotherapy. Relapsed disease was defined by reappearance of myeloid blasts in either the peripheral blood or bone marrow following obtaining a CR.

Patient characteristics reviewed included age, gender, race, history of antecedent hematologic disorder, diagnostic classification by FAB and World Health Organization (WHO) criteria, cytogenetic risk group, prior induction therapy, and history of HCT. Review of cytogenetic status included karyotype based on a minimum of 20 metaphase cells

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TABLE I. European Prognostic Index[a]

Prognostic factor	Points
RFI, relapse-free interval from first complete remission	
>18 months	0
7–18 months	3
<7 months	5
CYT, cytogenetics at diagnosis	
t(16;16) or inv(16)[b]	0
t(8;21)[b]	3
Other	5
AGE, age at first relapse	
<36 years	0
36–45 years	1
>45 years	2
SCT, stem-cell transplantation before first relapse	
No SCT	0
Prior SCT (autologous or allogeneic)	2
Total Score = RFI + CYT+ AGE + SCT	
Favorable risk group	0–6
Intermediate risk group	7–9
Poor risk group	10–14

[a] Adapted from Breems et al. 2005.

[b] With or without additional cytogenetic abnormalities.

from the bone marrow or peripheral blood, if bone marrow analysis was not available, for clonal structural abnormalities including t(15:17)(q22;q12), t(8:21)(q22;q22), inv(16), and t(16:16). Molecular analysis by fluorescence in situ hybridization and polymerase chain reaction included *FLT3-ITD*, *NPM1*, *CEBP*A, and *MLL* rearrangements at the discretion of the physician. Karyotypes were divided into favorable karyotypes [t(15:17), t(8:21), inv(16)(p13.1q22) or t(16;16)(p13.1;q22)], unfavorable karyotypes [complex karyotype (≥3 abnormalities, −5, del(5q), −7, del(7q), 3q abnormality, 11q23 anomaly, t(9:22)(q34;q11.2), t(6:9)(p23;q34)], or intermediate (all other abnormalities). At the start of second-line MEC chemotherapy, patient and disease characteristics recorded included disease status, length of prior response, white blood count, and peripheral blood blast percentage.

Induction and postremission therapy. All patients received first-line therapy with standard induction regimens including idarubicin and cytarabine, idarubicin and high-dose cytarabine or daunorubicin and cytarabine. Dosing and schedules were as previously described; idarubicin 12 mg/m^2/day, days 1–3; cytarabine 100 mg/m^2/day, days 1–7 [11–13]; idarubicin 12 mg/m^2/days, days 1–3; and cytarabine 3000 mg/m^2 every 12 hr, days 1–4; [14] daunorubicin 45 mg/m^2/day, days 1–3 and cytarabine 100 mg/m^2/day, days 1–7 [15]. Among patients who obtained a CR to induction, postremission therapy consisted of two cycles of idarubicin or daunorubicin and cytarabine or four cycles of high-dose cytarabine.

Second-line MEC chemotherapy. Second-line MEC chemotherapy included mitoxantrone intravenous push at 8 mg/m^2/day, etoposide intravenous over 2 hr at 100 mg/m^2/day, and cytarabine 1,000 mg/m^2/day with all three agents repeated days 1–5. The infusion schedule was as described previously, including administration of etoposide, followed by cytarabine and lastly intravenous push of mitoxantrone [6]. No growth factors, antiviral, antibiotic, or antifungal therapy were provided as routine prophylaxis, although could be provided at physician discretion.

Response assessment. International Working Group criteria defined response following a single cycle of second-line MEC chemotherapy including CR (neutrophils > 1,000/μl, platelets > 100,000/μl, and bone marrow blasts <5%), CR with incomplete recovery (CRi, all CR criteria except residual neutropenia < 1,000/μl, or thrombocytopenia < 100,000/μl), morphologic leukemia-free state (MLFS, neutrophil, and platelet counts not evaluable, bone marrow blasts < 5%), partial remission (neutrophils > 1,000/μl, platelets > 100,000/μl, bone marrow blasts decrease by >50% but not less than 5% or decrease by 5–25%) [10,16]. OS following second-line MEC chemotherapy was defined from day of second-line induction to death from any cause or last follow-up.

Anticipated response and survival rates were calculated by risk stratification of patients using the European Prognostic Index (EPI) described Breems et al. [17] The four parameters included in the EPI include the length of relapse-free interval after first complete remission, cytogenetics at diagnosis, age at relapse, and whether previous stem-cell transplantation was performed (Table I). All patients were scored according to EPI criteria, and anticipated rates of response and survival were determined based on percent of patients with favorable-, intermediate-, and poor-risk disease.

TABLE II. Patient and Disease Characteristics

Characteristics	n = 77
Age, years	
Median (and range)	54 (18–78)
<60 years, *n* (%)	56 (73)
Gender, male/female	53/24
Race, *n* (%)	
White	60 (78)
Black	3 (4)
Asian	11 (14)
Other	3 (4)
Antecedent hematologic disorder, *n* (%)	13 (17)
FAB, *n* (%)	
M0	19 (25)
M1	9 (12)
M2	8 (10)
M4/M4eo	18 (23)
M5a/M5b	10 (13)
M6	1 (1)
Unclassified	30 (39)
WHO classification, *n* (%)	
AML with recurrent genetic abnormalities	35 (45)
AML with myelodysplasia-related changes	17(22)
AML, not otherwise specified	24 (31)
Therapy-related myeloid neoplasms	1 (1)
Cytogenetic risk group, *n* (%)	
Favorable	4 (5)
Intermediate	49 (64)
Poor	21 (27)
Unknown	3 (4)
Prior induction chemotherapy regimen, *n* (%)	
Idarubicin and cytarabine	10 (13)
Idarubicin and high-dose cytarabine	44 (57)
Daunorubicin and cytarabine	5 (7)
Unknown	18 (23)
Prior bone marrow transplant, *n* (%)	3 (4)
Disease status, *n* (%)	
Refractory	35 (46)
Relapsed, 1st	41 (53)
Relapsed, >1	1 (1)
Length of prior response, days	
Median (and range)	115 (13–1201)
Prior response >6 months, *n* (%)	16 (21)
White blood count at treatment, cells/uL	
Median (and range)	1.15 (0.1–180)
Peripheral blood blast % at treatment, %	
Median (and range)	5 (0–98)
ECOG performance status	
0–1	54 (70)
2–4	19 (25)
Unknown	4 (5)
European prognostic index score, *n* (%)	
Favorable-risk	1 (1)
Intermediate-risk	10 (13)
Poor-risk	66 (86)
Follow-up, days	
All patients, median (and range)	153 (10–2235)
Patients alive at last follow-up, median (and range)	171 (28-2178)

Statistical analysis. The clinical variables reported descriptively included age, gender, race, antecedent hematologic disease, FAB and WHO classifications, prior induction therapy, length of prior response, white blood count, and percent peripheral blasts at treatment. Clinical variables tested for potential prognostic value based on prespecified hypotheses were disease status at time of second-line chemotherapy and cytogenetic risk as prognostic of response to MEC chemotherapy and OS. Association with EPI and putative prognostic variables with response was assessed by X^2 statistic and OS probabilities according to the Kaplan–Meier method. Statistical analysis was performed using open-source software R (www.r-project.org) with a *P*-value of 0.05 considered significant.

Results

Patient characteristics

Characteristics of the 77 patients are summarized in Table II. Median age was 54 years and 73% of patients were less than 60 years. The majority of patients (70%) were male and Caucasian (78%). Thirteen patients had an antecedent hematologic disorder including 10 patients with prior diagnosis of myelodysplastic syndrome, one patient with a

TABLE III. Patient Outcomes

Outcome	Total (n = 77)	Disease status: Refractory (n = 35)	Disease status: Relapsed[b] (n = 42)
Aplasia marrow, *n* (%)			
Hypocellular	50 (65)	22 (63)	28 (67)
Hypercellular	14 (18)	8 (23)	6 (14)
Not performed	13 (17)	5 (14)	8 (19)
Remission marrow, *n* (%)			
Treatment failure	57 (74)	28 (80)	29 (69)
Complete response	14 (18)	4 (11)	10 (24)
Morphologic leukemia-free state	6 (8)	3 (9)	3 (7)
Overall response	20 (26)	7 (20)	13 (31)
Remission achieved with salvage therapy[a]	10 (18)	5 (18)	5 (18)
Alive at last follow-up, *n* (%)	23 (30)	8 (23)	15 (37)

[a] Following MEC treatment failure (rate reported among patients with treatment failure following MEC).

[b] 41 of 42 patients in first relapse. 1 of 42 in second relapse.

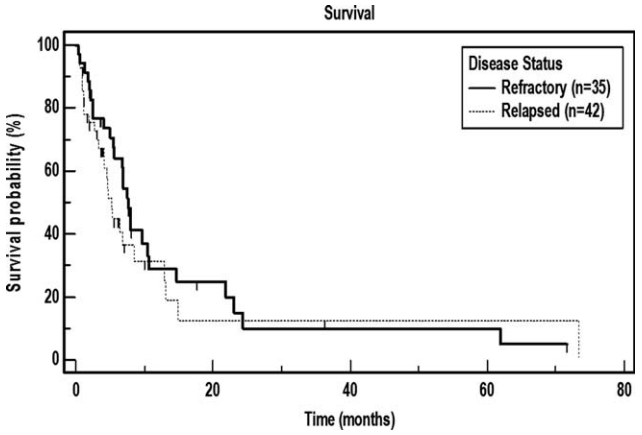

Figure 1. Survival stratified by disease status at second-line therapy. Kaplan–Meier plot of disease status-stratified overall survival.

prior diagnosis of chronic myelomonocytic leukemia, one patient with a prior history of pancytopenia, and one patient with a history of non-Hodgkin lymphoma (follicular histology). By the revised WHO classification, the majority of patients had AML with recurrent genetic abnormalities, 45%, and by FAB classification most patients either had M0 or M4/4eo subtype (25% and 23%, respectively). Only 5% of patients had favorable cytogenetic risk, with intermediate risk representing the majority of patients (64%). The majority of patients (86%) had poor-risk disease by EPI stratification, and only 1 of 77 patients had favorable-risk disease by this criterion.

At the time of second-line MEC chemotherapy, 41 of 42 patients had relapsed after their first CR (one patient with relapse beyond first CR), and 35 patients were refractory to induction therapy. For all but one of the patients previously achieving CR, MEC represented the primary regimen for reinduction of remission. Among those obtaining a prior CR, median duration of response was 115 days with three patients receiving allogeneic HCT before relapse and MEC chemotherapy. Median percentage of peripheral blood blasts at relapse was 5% though range extended to 98%. Evaluable period of follow-up was 153 days with range of up to 2,235 days.

Efficacy and toxicity of second-line MEC chemotherapy

Clinical outcomes of MEC chemotherapy for relapsed or refractory AML are listed in Table III. Overall, 18% of patients obtained a CR and 8% a MLFS, resulting in an overall response rate of 26%. Initial evaluation, 7 days after completion of MEC chemotherapy, demonstrated inadequate aplasia among 14 of 64 patients evaluated. As previously observed, adequate aplasia did not correlate with remission as 74% of patients failed MEC chemotherapy and required additional second-line therapy if tolerated. Ten patients, 18%, achieved a remission following subsequent therapy, which included gemtuzumab, FLAG-ida (fludarabine, cytarabine, G-CSF, and idarubicin), and additional reinduction with MEC. Consolidation therapy postremission with second-line MEC included allogeneic HCT in 50%, autologous HCT in 5%, MEC consolidation in 20%, and consolidation idarubicin or daunorubicin and cytarabine in 25% of patients.

Twenty-three patients were alive at a median follow-up of 171 days (range, 28–2,178 days). Median OS was 6.8 months with 12-month and 36-month OS of 28.6% and 10.9%. Notably, all patients alive at 36 months received an autologous or allogeneic HCT consolidation following second-line MEC and achieving a CR2. Collectively, 30-day mortality was only 10.4%. In total, 8, 15, and 19 patients died during the 30, 60, and 90 days, whereas ~30% of these deaths were caused by infectious complications (four bacterial and two viral in etiology), and the majority, 85%, of remaining deaths were due to the underlying disease. Overall, treatment-related mortality (TRM; nonrelapse related deaths) due to MEC occurred in only 6.5% of patients.

To adjust for the risk status of our cohort, the anticipated rates of CR and OS were calculated based on risk stratification using the EPI index (Table I) [17]. The anticipated rates of CR and 1-year OS by the EPI for our cohort, calculated based on the percentage of patients with EPI favorable-, intermediate-, and poor-risk disease, were 29% (CR) and 52% (1-year OS). The observed CR rate, 18%, and 1-year OS, 28.6%, was significantly inferior to anticipated outcomes by EPI ($P < 0.01$). This observation was present among patients less than 60 years of age as well, with an inferior CR rate, 31%, and 1-year OS, 21%, observed in our series compared to that anticipated by the EPI, 39% and 53%, respectively ($P < 0.01$). Among our series of 77 patients, 5-year OS of 10.9%, however, was similar to the anticipated outcome by EPI of 9.6% ($P = 0.79$).

Prognostic factors

Cytogenetic risk and disease status were evaluated for their ability to predict response to and survival following MEC chemotherapy. Overall, response rates by cytogenetic risk were not significantly different with 50% of favorable, 27% of intermediate, and 23.8% of poor risk cytogenetic patients achieving either a CR or MLFS ($P = 0.51$). Also, median OS was similar between different cytogenetic groups (8.3, 6.8, and 4.7 months, respectively) ($P = 0.66$). Patients with t(8:21) or chromosome 16 abnormalities had similar response rates and survival.

Disease status at the time of induction with second-line MEC chemotherapy failed to predict response or survival ($P = 0.41$ and $P = 0.36$, respectively). Twenty percent of patients with refractory disease obtained a CR or MLFS compared to 31% of patients with relapsed disease (Table III). Five patients with relapsed and five with refractory disease were able to obtain remission with additional lines of therapy. No difference was observed among patients with relapsed versus refractory disease, 37% compared to 23% of patients were alive at last follow-up. Median OS was 5.3 versus 7.6 months, $P = 0.36$, and 36-month OS was 12.6% versus 9.9% (see Fig. 1).

Discussion

The majority of patients with AML obtaining a response to induction chemotherapy will require second-line therapies within 12 months for relapsed disease. Despite this,

TABLE IV. Outcome Following MEC Chemotherapy for Relapsed/Refractory AML

Author (Year)	*n*	Complete response rate (%)	Overall survival		
			Median (weeks)	1-year (%)	5-year (%)
Amadori et al. (1991)	32	66	36	NR	NR
Archimbaud et al. (1995)	133	60	33	NR	11
Vignetti et al. (1996)	50	68	NR	NR	29[a]
Greenberg et al. (2004)	63	19[b]	25	NR	NR
Feldman et al. (2005)	97	28	22	NR	NR
Current series	77	18[c]	32	29	11

NR, not reported.

[a] 70-month overall survival.

[b] Response rate following a single cycle of MEC chemotherapy.

[c] 26% response rate of CR + CRp.

no preferred second-line regimen has been adopted. Widely disparate reported outcomes for second-line regimens further complicate clinical decision making and clinical trial design without an accurate estimate of baseline response rate. The purpose of this study was to review all patients who received second-line mitoxantrone, etoposide, and cytarabine (MEC) chemotherapy at a single, tertiary care institution, outside of a clinical trial to determine response rate and survival following second-line therapy.

Similarly to previously described in Ref. 17, our patients were relatively young (median age of 54 years and ~3/4 of patients were ≤60 years), 17% had an antecedent hematologic disorder and the majority had intermediate risk cytogenetics at the time of relapse. Although we observed higher responses (50%, 27%, and 23%) and survival (8.3, 6.7, and 4.7 months) in patients with favorable risk cytogenetic groups, the limited sample size and magnitude of effect was not statistically significant. These effects resemble previously described results, where MEC chemotherapy was chosen as the backbone for clinical trials [8].

The treatment-related toxicity of second-line MEC chemotherapy in our cohort was similar or less than that observed in the original series. Of deaths within the first 90 days in our series, 25% were attributed to toxicity of therapy including infectious complications. Overall, TRM in our series was 6.5%. Despite apparent advances in supportive care, TRM as a potential effect modifier explaining the variability in outcomes, because the original MEC series, which reported TRM of 6.3–14%, may not be effecting clinical outcomes as anticipated [6–8,18,19].

Almost half (45%) of the patients in our cohort were refractory to conventional induction chemotherapy at the time of MEC therapy. The CR rates and median OS observed in our cohort compare adversely with previously described patients treated in similar regimens in the refractory setting (CR rate 11% with ORR 20% in our series vs. 53% as reported by Brandwein et al. and median OS 7.6 vs. 9.2 months, respectively) [20]. Similar response rates have been previously reported with MEC therapy in refractory, as well as relapsed, patients as reported in recent trials (Table IV). Most of our patients with relapsed disease had poor risk features (CR duration of <6 months in ~80% of patients). Although the overall response rates were higher among relapsed compared to refractory patients, these differences did not reach statistical significance (37% vs. 23%, $P = 0.41$). These results support the need for better individual patient risk stratification when analyzing results of uncontrolled clinical trials.

To address this issue and to control for the risk status of our series compared to prior reported outcomes of patients receiving reinduction regimens, we stratified our cohort by the EPI. A limitation in applying the EPI to our series is that the EPI was developed among a series of relapsed patients' ages 15–60 years. After stratification, our observed CR of 18% was inferior to that anticipated by EPI criteria (29%) among all patients and among those less than 60 years of age (31% compared to 39%). However, the 5-year OS of 11% in our cohort was not significantly worse than the calculated 5-year OS based on the EPI (9.6%). Thus, our poor 5-year OS can be partially explained by the inclusion of refractory patients and the presence of very high-risk features in our patient population, and it further demonstrates the need for appropriate risk stratification in patients with relapsed AML. Increased incorporation of EPI or other prognostic indices in treatment decisions of patients with relapsed AML will allow improved stratification of therapy based on level of risk. For at-risk patients, our results further confirm that stem cell transplant appears to be required for long term disease control following first relapse.

Two main questions arise from this and other recent studies: Why are current results using MEC chemotherapy so discordant with the original report? and should MEC be the preferred salvage regimen for patients with relapsed AML? We believe that two primary reasons are responsible for these discordant clinical outcomes. The first relates to patient selection. Risk stratification criteria were poorly recognized and documented at the time of the original report. Most patients were younger, karyotype analyses were not routinely performed, and time to relapse was poorly defined. Thus, it is reasonable to speculate that these patients had relatively low-risk disease at the time of MEC therapy. Second, modifications to the original MEC regimen have been made through the years. For example, only 5 days have been used in recent studies [8], and the doses and schedule of the agents have also been modified [8]. Although, only well-designed clinical trials, with appropriate pretreatment risk stratification assessment, will be able to answer what is the optimal salvage regimen for relapsed AML, several recently presented data suggest other regimens may have more activity than MEC in this setting [21,22].

In conclusion, we report a single institution series where MEC salvage chemotherapy produced unacceptably low overall response rates and short median OS. Recognizing these low-response rates and the role of individual patient risk at the time of relapse may improve comparison of uncontrolled clinical trials and development of better salvage regimens for these patients.

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