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Salvage therapy with mitoxantrone, etoposide and cytarabine in relapsed or refractory acute lymphoblastic leukemia

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ABSTRACT

The survival of patients with relapsed or refractory acute lymphoblastic leukemia (ALL) is poor. We performed a retrospective analysis of 40 patients treated with five days of mitoxantrone 8 mg/m^2/day, etoposide 100 mg/m^2/day, and cytarabine 1000 mg/m^2/day (MEC). The complete remission rate was 30% and median remission duration was 11.2 months. Median overall survival was 6.5 months. In univariate analysis, patients in first relapse had improved overall survival compared to ≥second relapse ($p = 0.02$). Thirty-day mortality rate was 7.5%. In relapsed or refractory ALL, MEC demonstrated moderate activity, but did not improve survival compared to published salvage chemotherapy regimens.

1. Introduction

During recent decades, intensification of chemotherapy and risk-adapted treatment approaches have resulted in steady improvement in upfront treatment outcomes of patients with ALL, with cure rates now approaching 90% and 40% for pediatric and adult ALL, respectively [1,2]. In contrast, the prognosis for relapsed or refractory ALL has remained poor, and while some pediatric protocols achieve long term disease-free survival of 10–60%, relapsed ALL in adults is regarded as an almost incurable disease [3,4]. The primary goal of reinduction chemotherapy is cytoreduction or attainment of a second or subsequent remission, crucial both for short-term survival as well as eligibility for allogeneic hematopoietic stem cell transplantation (HCT) [5]. While HCT represents the sole potentially curative treatment modality, it is only available to a highly selected group of patients.

Commonly used salvage chemotherapy regimens include cycle B of hyperCVAD (methotrexate and cytarabine) [6], MEC (mitoxantrone, etoposoide, and cytarabine) [7–9], high dose cytarabine, or FLAG (fludarabine, cytarabine, and granulocyte stimulating factor)-idarubicin [10–14]. Like many of these regimens, MEC was originally developed for relapsed AML [7], but has also been investigated in ALL, with disappointing results [8]. Recently, several Phase I and II studies have demonstrated promising activity for naked and conjugated monoclonal antibodies in relapsed ALL (epratuzumab, inotuzumab, blinatumomab) [15–17], and randomized Phase III trials are being conducted to compare these novel agents with traditional chemotherapy-based regimens. However, there is no standard of care salvage chemotherapy regimen for relapsed/refractory ALL and there are limited data available for chemotherapeutic regimens to serve as a comparison for novel immunotherapies. In this study, we retrospectively reviewed the data of 40 patients with relapsed or refractory ALL who received reinduction chemotherapy with MEC. The aims of the study were to analyze the efficacy and toxicity of this commonly used salvage regimen in the current era of diagnosis and supportive care at a tertiary care institution.

2. Materials and methods

2.1. Patients

This is a retrospective study of 40 consecutive adult patients age 18 years or older who received MEC chemotherapy at the Stanford Cancer Institute for relapsed or refractory ALL (T or B cell) between November 2003 and April 2013. The regimen was chosen at the discretion of the treating physician. The study was approved by the Institutional Review Board of Stanford University's Research Compliance Office through a waiver of consent. Refractory disease was defined as failure to achieve CR, as defined below, following induction therapy. Relapsed disease was defined by reappearance of leukemic blasts in bone marrow, peripheral blood, or an extramedullary site following a CR.

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Patient characteristics reviewed included age, gender, race, diagnostic classification by World Health Organization (WHO) criteria, prior treatment regimens, karyotype [18], BCR-ABL status, and history of HCT. Additional patient and disease characteristics recorded prior to the start of salvage MEC chemotherapy included disease status, duration of prior response if any, white blood cell count, and peripheral blood blast percentage.

2.2. Induction and postremission therapy

All patients received first-line induction therapy with standard induction regimens including CALGB 8811 [19], CALGB 9511 [20], hyper-CVAD [21], or as per clinical trial. Patients who achieved a CR subsequently received consolidation and prolonged maintenance on the respective treatment protocol, or allogeneic hematopoietic cell transplant. Patients with Philadelphia chromosome positive ALL received imatinib in addition to chemotherapy.

2.3. Salvage MEC chemotherapy

Salvage MEC chemotherapy consisted of mitoxantrone 8 mg/m^2/day intravenous push, etoposide 100 mg/m^2/day intravenous over 2 h, and cytarabine 1000 mg/m^2/day intravenous over 2 h, with all three agents repeated on days 1–5 [7]. Growth factors and antimicrobial prophylaxis was provided at the discretion of the treating physician.

2.4. Response assessment

CR was defined as attainment of M1 bone marrow (less than 5% blasts) with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral counts (absolute neutrophil count above 1000/μl and platelet count above 100,000/μl). CR with incomplete recovery (CRi) included all CR criteria except absolute neutrophil countless than 1000/μl or platelet count less than 100,000/μl. Partial remission (PR) was defined as complete disappearance of circulating blasts, no evidence of extramedullary disease, and achievement of M2 bone marrow status (equal or more than 5% but less than 25% blasts, and adequate cellularity) with recovery of peripheral counts as above. Progressive disease (PD) was defined as an increase of at least 25% in the absolute number of leukemic cells in the peripheral blood or bone marrow, or the development of extramedullary disease. Patients not fulfilling criteria for CR, PR, or PD were considered to have stable disease (SD). Overall survival following MEC chemotherapy was defined from first day of treatment to death from any cause or last follow-up. Patients who were alive or lost to follow-up were censored at the time last seen alive. Duration of response was defined from the date of CR until disease relapse.

2.5. Statistical analysis

The clinical variables reported descriptively included age, gender, race, WHO classification, prior treatment regimens, duration of prior response, white blood count, and percent peripheral blasts prior to treatment. Continuous variables were summarized by their medians and standard deviations and categorical variables were summarized by proportions. Clinical variables assessed for potential prognostic value in assessing response to MEC chemotherapy and survival outcomes included relapse number $\leq$1, duration of first CR >12 months, duration of CR with last therapy >12 months, unfavorable risk cytogenetics, ALL subtype (B versus T cell), WBC >30 $\times$ 10^9 at the time of relapse in B cell ALL, WBC >100 $\times$ 10^9 at the time of relapse in T cell ALL, and age <35 years and <55 years. Unfavorable risk cytogenetics were defined as *t*(9;22), *t*(4;11), *t*(8;14), complex karyotype with >5 abnormalities, hypodiploidy, or near triploidy. Overall survival and relapse-free survival (RFS) probabilities were estimated with the Kaplan–Meier estimators. The log-rank test was used for comparisons of survival probabilities. Multivariate Cox hazard regression models were used to adjust time-to-event endpoints for potential confounders. Proportionality assumptions were satisfied in applying the Cox models to the time to event data. All *p* values are 2-sided with a significance level of 0.05. All statistical analyses were performed using R1.10.1 (The R foundation for statistical computing).

3. Results

3.1. Patient characteristics

Characteristics of the 40 patients are summarized in Table 1.

Most patients had pre-B acute lymphoblastic leukemia. Six (15%) patients had *t*(9;22) or Philadelphia positive disease by molecular analysis, and 3 (7.5%) additional patients had other unfavorable cytogenetics, including 1 with *t*(4;11) and 2 with complex karyotype. Thirty-three percent of patients had a normal diploid karyotype. Thirty-five patients had achieved a CR after their initial induction treatment (CR1) with a median duration of CR1 of 9.9 months. At the time of salvage MEC chemotherapy, most patients (60%) had relapsed after their first CR. Patients had received a median of 2 (range 1–4) treatments prior to MEC, including stem cell transplantation in 3 cases. Median number of treatments was higher than expected due to many patients being refractory and requiring multiple lines of therapy. Among patients who had achieved a CR with their last treatment prior to MEC salvage, the median duration of response was 7.5 months (1.4–63.6 months).

Table 1
Patient characteristics.

Patient characteristic	Outcome
Age, years	
Median (and range)	35.5 (18–68)
<60 (%)	34 (85)
Gender, *n* (%)	
Male	25 (62.5)
Female	15 (37.5)
Race, *n* (%)	
White	18 (45)
Latino	12 (30)
Asian	2 (5)
Black	1 (3)
Other/unknown	7 (17)
ALL subtype, *n* (%)	
Pre-B	33 (82.5)
T	3 (7.5)
Burkitt's	1 (2.5)
Other (stem cell/bilineage)	3 (7.5)
Relapse number, *n* (%)	
0 (CR never achieved)	5 (12.5)
1	24 (60)
2	8 (20)
3	3 (7.5)
Median number of previous regimens (range)	2 (1–4)
Previous regimens, *n* (%)	
CALGB 8811/9511	24 (60)
HyperCVAD	22 (55)
BMT	3 (7.5)
WBC at relapse	
Median (range)	6.2 (0–213)
>30 $\times$ 10^9/L (B cell), *n* (%)	11 (33)
>100 $\times$ 10^9/L (T cell), *n* (%)	1 (33)
Cytogenetic risk group,[a] *n* (%)	
Unfavorable	9 (22.5)
Ph+	6 (15)
Other	20 (50)
Unknown or analyzable metaphases not present	11 (27.5)
Median duration of CR1, months (range)	9.9 (1.5–104.4)

[a] Based on Moorman et al. Blood. (2007) 109: 3189–3197.

3.2. Efficacy and 30-day mortality of salvage MEC

Clinical outcomes of 40 patients with relapsed or refractory ALL treated with MEC chemotherapy are shown in Table 2.

Overall, 12 (30%) patients achieved a CR with MEC, of which 3 did not receive further therapy, 4 received consolidation with

Table 2
Clinical efficacy and 30-day mortality.

Clinical endpoint	Outcome
Median follow-up, months (range)	4.3 (0.4–61.1)
CR achieved, *n* (%)	
Yes	12 (30)
No	26 (65)
Unknown	2 (5)
Median duration of response, months (range)	11.2 (0.5–57.8)
Subsequent therapy, *n* (%)	
BMT	10 (25)
MEC	6 (15)
Other chemotherapy	12 (30)
Median OS for all patients, months (range)	6.5 (0.4 – not reached)
30-day mortality, *n* (%)	3 (7.5)