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Dose-intense etoposide–cyclophosphamide without stem cell transplantation for patients with intermediate and high cytogenetic risk primary refractory and relapsed acute myeloid leukemia

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ABSTRACT

Dose-intense etoposide–cyclophosphamide (D-I ECy) without stem cell transplantation has been used in salvage regimens for the treatment of resistant acute myeloid leukemia(AML). Previous D-I ECy studies classified AML according to FAB-criteria, before cytogenetic risk was found to be a major determinant of prognosis. Currently the influence of karyotype on response to D-I ECy is unknown. Thus, an observational study was conducted in thirty four patients treated with D-I ECy for resistant AML. The results show this regimen is moderately effective in achieving CR in relapsed AML patients, including those with age >60 and poor cytogenetic risk category.

1. Introduction

Standard induction treatment with anthracycline based regimens for patients with acute myeloid leukemia (AML) achieves complete remission(CR) in 60–80% patients [1]. Outcomes for patients with primary induction failure (PIF) and relapsed acute myeloid leukemia (Rel-AML) treated with chemotherapy alone are poor. Salvage regimens have variably been shown to achieve short term CR as a temporizing treatment prior to allogeneic stem cell transplantation [2]. Etoposide(E) and cyclophosphamide(Cy) are non-cross resistant chemotherapy agents frequently used in the treatment of many hematologic malignancies and routinely incorporated in autologous and allogeneic stem cell transplantion preparative regimens [3–8]. In limited case series, dose-intense etoposide–cyclophosphamide in combination (D-I ECy), without stem cell transplantation (HSCT) has successfully been used as salvage therapy for the treatment of resistant acute myeloid leukemia. Differences in etoposide and cyclophosphamide dose amongst the previously published studies has been a limitation in the evaluation of D-IECy [9–15]. Additionally, prior D-I ECy studies were conducted before cytogenetic and molecular mutations were found to be major determinants of prognosis. Currently, the influence of karyotype on response to D-I ECy is unknown. Thus, an observational study was conducted to determine treatment response to D-I ECy therapy in thirty-four consecutive, heavily pretreated PIF or Rel-AML patients with intermediate and unfavorable cytogenetics. All DI-ECy patients treated at NMH during the study period are included in the study.

2. Methods

Thirty-four consecutive adult patients diagnosed with PIF or Rel-AML treated with D-I ECy at Northwestern Memorial Hospital between 10/2004–12/2011 were enrolled in this study. The diagnosis of AML was confirmed by bone marrow biopsy according to WHO diagnostic criteria for hematologic malignancy [16]. Cytogenetic risk (good, intermediate and unfavorable) was defined according to published guidelines [17]. Thirty three patients received initial induction therapy with standard "7 plus 3" regimen (daunorubicin 45–90 mg/m^2 IV bolus on days 1–3 and cytarabine 100 mg/m^2 by continuous infusion over days 1–7). CR was defined as <5% blasts in the bone marrow 28 days after "7 plus 3" was administered. If CR was achieved, patients generally received consolidation therapy with 1–3 courses of high-dose cytosine arabinoside (HIDAC). A limited number of patients subsequently underwent SCT before receiving D-I ECy. Amongst the thirty-four patients included in this study who were either PIF after initial induction, or relapsed after consolidation treatment(s), twenty seven patients were treated with D-I ECy according to the following schedule: Etoposide 3 gm/m^2 was given by continuous infusion over 48–72 h, immediately followed by cyclophosphamide 50 mg/kg iv over 3 h daily for 3 or 4 days(150–200 mg/kg total dose). The other seven D-I ECy treated patients received a lower etoposide dose, 1.8–2.4 gm/m^2 over 48–72 h followed by cyclophosphamide 50 mg/kg iv over 3 h for 3 or 4days. The decision to use a higher or lower D-I ECy dose, or the order in which D-I ECy was given relative to other salvage regimens was determined at the discretion of the attending hematologist. All patients received acyclovir, an azole antifungal agent, and flouroquinolone antibiotic for prophylaxis beginning at the time of D-I ECy administration.

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Table 1
Demographics for etoposide–cyclophosphamide treated patients.

Characteristic	Number(%)
Number	34
Age	48(25–70)
Age > 60	10(29)
Male	14(41)
Indication	
Primary refractory AML	13(38)
Relapsed AML	21(62)
Initial CR duration(months)	8(2–72)
Cytogenetic risk category	
Good	3(9)
Intermediate	12(35)
Normal karyotype	8/12(67)
Unfavorable	19(56)
Complex karyotype	6/19(32)
del(5) ± monosmy 7	6/19(32)
HSCT prior to etoposide–cyclophosphamide	5(15)
Etoposide–cyclophosphamide prior to HSCT	12(35)
Prior exposure to high-dose cytarabine	25(75)
Number of salvage regimens prior to etoposide–cyclophosphamide	
0	12(35)
1	13(38)
>1	9(27)
Etoposide–Cyclophosphamide Dose Level	
E(1.8–2.4 g/m^2) and Cy(150–200 mg/m^2)	7(20)
E(3 g/m^2) and Cy (150–200 mg/m^2)	27(80)

Comparison of percentage rates was based upon Chi-Square or Fisher exact test for sparse numbers. *t*-test was used to test the difference between continuous data variables. Survival data was based upon Kaplan–Meier Curve and Cox proportional hazard model.

3. Results

Patient demographics are shown in Table 1. Most D-I ECy patients were treated for Rel-AML (62%), had had previous exposure to high or intermediate-dose cytarabine (75%), age <60 (70%), classified as intermediate or unfavorable cytogenetics (92%), and had received at least 1 salvage regimen(in addition to induction and consolidation) prior to receiving D-IECy (65%).Amongst the four karyotypes identified in patients with intermediate-risk cytogenetics, 67% had normal karyotype. Complex karyotype (32%) and Del(5q) and/or monosomy 7(32%) were the two most frequent karyotypes amongst the seven cytogenetic abnomalities seen in patients with high-risk cytogenetics. Median length of first remission was eight months(range: 2–72 months).

Patient outcomes are shown in Table 2. Overall CR was achieved in 32% of D-I ECy treated patients. Rel-AML cases achieved significantly higher CR rates compared to PIF cases (48 versus 8% respectively, $p < 0.0145$). Median CR duration after D-I ECy treatment was 5 months. Overall survival is based upon the Kaplan–Meier curve (Fig. 1). No significant difference in response was found with regard to patient age (>60 versus < 60 years, $p < 0.3085$), gender ($p < 0.1345$), prior exposure to intermediate or high dose cytarabine, ($p < 0.4254$), or the number of salvage regimens received prior to D-I ECy, ($p < 0.1672$). Subset analysis shows unfavorable karyotype (Fig. 2) to be associated with poorer response ($p < 0.0223$). Etoposide dose intensity was not associated with improved CR, ($p < 0.5172$) (Fig. 3). Grade 3–4 gastro-intestinal toxicity was observed in 19 (59%) patients, which was not associated with etoposide dose level ($p < 0.99$). Thirty seven microbiologically confirmed infections occurred in 26 (76%) patients, and was not associated with etoposide dose level ($p < 0.4123$). Treatment related mortality was observed in 6 (18%) patients.

Table 2
Complete remission in patients treated with dose-intense etoposide–cyclophosphamide.

Overall CR(%)	11/34(32)
CR duration(months)	5
	1/13(8)
Response to D-I ECy	
Primary Refractory AML	
Relapsed AML	10/21(48)
Response to D-I ECy by dose level	
ECy (1.8-2.4 gm/m^2)	1/7(14)
ECy(3 gm/m^2)	10/27(37)
Response to D-I ECy by karyotype	
Favorable	3/3(100)
Intermediate	2/12(17)
Poor	6/19(32)
Response to D-I ECy age	
>60	3/10(30)
<60	8/24(33)
Response to D-I ECy by the number prior salvage treatments	
0	3/12(25)
1	5/13(38)
2	1/7(17)
3	2/2(1000
Grade 3–4 gastro-intestinal toxicity	19/34(59)
Microbiologically confirmed infection	37
Gram negative organisms	11
Clostridium difficile	4
Gram positive organisms	14
Fungal(mold)	6(4)
Polymicrobial	10
HSV	2
Treatment related mortality	6/34(18)

4. Discussion

The treatment of patients with primary refractory and relapsed AML remains challenging. Complete remission rates and long term survival following salvage therapy is very poor. The possibility of achieving CR in resistant AML has been shown to decrease with each additional salvage treatment, and the only potentially curative treatment for patients with PIF and Rel-AML is allogeneic stem cell transplantation, which, in order to be successful, requires patients be in CR prior to transplantation [19]. Several salvage regimens are currently used for patients with PIF and Rel-AML, none of which has been shown superior, and the treatment for PIF AML and Rel-AML is largely based upon institutional preference

We empirically treated thirty four PIF and Rel-AML patients with D-I ECy according to a relatively fixed dose schedule of etoposide and cyclophosphamide, with limited dose modifications primarily based upon performance status. The results show this regimen was moderately effective for treating relapsed AML. These results are encouraging for heavily pre-treated patients including those >60 and with unfavorable cytogenetics who historically, are known to be very poor responders to salvage treatment.

During the 1980s, dose escalation studies using etoposide and cyclophosphamide as single agents, or in combination, showed these 2 drugs to be effective for treating a number of different refractory hematological diseases when given at doses much higher than conventionally used. Notably, Brown et al., treated 71 patients with hematological malignancies with dose-intense ECy and determined the maximally tolerated dose of etoposide (dose limiting gastro-intestinal mucositis at 4.2 gm/m^2) and cyclophosphamide (dose limiting cardiac toxicity at 200 mg/kg)) when given in combination for resistant hematological malignancies without requiring stem cell support.

Within the study cohorts, 40 Rel-AML patients were treated across several dose tiers. CR was achieved in 40% of patients with refractory AML but unfortunately the study results did not report the number of Rel-AML patients and CR rate within each dose tier