Optimum Induction Chemotherapy for Pediatric Acute Myeloid Leukemia: Experience From A Developing Country

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OBJECTIVES Treatment outcome in children with acute myeloid leukemia (AML) has improved in the developed world but remains poor in developing countries. We assessed the role of etoposide in induction chemotherapy in pediatric AML.

METHODS This analysis retrospectively compared 2 induction chemotherapy regimens consisting of daunorubicin and cytarabine with etoposide (ADE) and without etoposide (AD). All newly diagnosed cases of AML younger than 18 years from January 1, 2012, onwards who completed their treatment before January 31, 2019, were included. Data of 186 cases, including 117 males (62.9%) and 69 females (37.1%), were analyzed. Demographic, initial presentation blood counts, and AML subtypes were almost identical in both groups.

RESULTS Complete remission rates were almost identical for the ADE versus the AD group (78.8% vs 80.0%, $p = 0.980$). Treatment-related mortality was higher, albeit not significantly, in the ADE (25 of 105; 23.8%) versus the AD (16 of 81; 19.8%) group ($p = 0.508$). Overall survival was 32 of 105 (30.5%) in the ADE and 43 of 81 (53.1%) in the AD group ($p = 0.079$), and disease-free survival was 29 of 105 (27.6%) and 39 of 81 (48.1%) in ADE and AD groups ($p = 0.056$), respectively.

CONCLUSIONS Etoposide in induction treatment of pediatric AML is associated with increased episodes of bacterial and fungal infections and high treatment-related mortality. Moreover, it does not offer any survival benefit. In low- and middle-income countries like Pakistan, it should not be used in the induction treatment protocol.

ABBREVIATIONS AD, daunorubicin and cytarabine; ADE, daunorubicin and cytarabine with etoposide; AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; DFS, disease-free survival; Fla-Ida, fludarabine, idarubicin, and cytarabine; LMIC, low- and middle-income countries; MRC, Medical Research Council; OS, overall survival; TRM, treatment-related mortality

KEYWORDS chemotherapy; developing country; etoposide; Pakistan; pediatric acute myeloid leukemia

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Introduction

Acute myeloid leukemia (AML) comprises 25% of childhood leukemia, with a yearly incidence rate of 5 to 7 cases per million.¹ In the 1950s complete remission (CR) was achieved by using mercaptopurine and methotrexate.² The combination of daunorubicin and cytarabine was introduced in the 1970s.^{3,4} This combination of cytarabine and anthracycline remains the backbone of induction chemotherapy in both pediatric and adult AML. The Medical Research Council (MRC) United Kingdom AML10 trial compared induction with cytarabine, daunorubicin, and etoposide (ADE) versus cytarabine and daunorubicin administered with thioguanine. The remission rate or disease-free-survival (DFS) was the same between the 2 arms of the study, although the thioguanine-containing regimen was more

toxic.⁵ The ADE regimen became the standard for children with AML in the United Kingdom and United States after this study.^{1,5} The MRC AML15 trial demonstrated that induction with daunorubicin and cytarabine (AD) resulted in equivalent survival rates when compared with ADE induction, and inclusion of etoposide provided no additional benefit in rate or durability of response.⁶ Based on these results, adult treatment protocols are not routinely using etoposide in the induction phase of chemotherapy.

Because of limited treatment facilities, poor socio-economic conditions and the unaffordability of treatment, and high treatment-related mortality (TRM), most children with AML are not treated in Pakistan. Moreover, there are no uniform national treatment protocols for pediatric oncology patients in the country. This study compares retrospectively the treatment results

of pediatric AML with and without etoposide use in induction phase of chemotherapy. There is a paucity of data on treatment outcomes in pediatric AML in low- and middle-income countries (LMICs); this study also highlights the problems faced in the LMICs by pediatric oncology centers.

Methods

The study was carried out at the pediatric oncology department of Combined Military Hospital, Rawalpindi, Pakistan. Combined Military Hospital is a military hospital primarily responsible for treating army personnel and their dependents. However, because of the scarcity of dedicated facilities for hematology and oncology in the country, a large number of civilians, especially from northern Pakistan, are also treated here.

This analysis retrospectively compared 2 induction chemotherapy regimens: ADE and AD. ADE chemotherapy was the main treatment protocol used during the initial 3 years of the study period. After analysis of treatment outcome with ADE, input from hematologists treating adult AML without etoposide, and literature review, AD chemotherapy was adopted for pediatric AML. There were no preferences for the ADE or the AD group before starting treatment. All newly diagnosed cases of AML younger than 18 years of age from January 1, 2012, onwards who completed their treatment before January 31, 2019, were included. Patients having acute promyelocytic leukemia, AML with Down syndrome, prior chemotherapy or leaving during treatment, and those who died before the start of chemotherapy were excluded. Patients having resistant disease who received fludarabine, idarubicin, and cytarabine (Fla-Ida) chemotherapy and patients who failed to get all 4 courses of chemotherapy were also excluded from final analysis. Study data included age, sex, blood counts at presentation, central nervous system disease status, French–American–British classification, immunophenotype, genetic abnormalities at diagnosis, chemotherapy protocol, treatment outcome, use of hematopoietic stem cell transplantation, last follow-up, and cause of death.

Detailed medical history and clinical examination were performed on each case. All of the patients were weighed at the time of admission before starting chemotherapy. The weight was recorded in kilograms and plotted on the standard World Health Organization Z-score chart for age and sex. The patients were categorized as adequately nourished, moderately malnourished, and severely malnourished if they had Z score below -2 , from -2 to less than -3 , and -3 or higher, respectively.

Diagnosis of AML was made on bone marrow (BM) morphology and flow cytometric immunophenotyping by standard techniques. Initial workup included full blood count, coagulation profile, and biochemical profile, including hepatic and renal function tests, and

cardiac function assessment by performing echocardiography. Response to chemotherapy was assessed by performing BM aspiration after recovery of blood counts. Cases were labeled as having CR, partial remission, and resistant/refractory disease per the following definitions. Complete remission was defined as $<5\%$ blasts in the BM; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $>1 \times 10^9/L$; platelet count $>100 \times 10^9/L$; and independence of red blood cell transfusions. Partial remission was defined as all hematologic criteria of CR plus decrease of BM blast percentage to 5% to 25% and decrease of pretreatment BM blast percentage by at least 50% . Resistant/refractory disease was defined as $>5\%$ blasts in the BM after 2 courses of induction treatment.

Therapy. Chemotherapy was based on the AML17 pediatric version adopted from the AML17 trial protocol of the MRC.

Induction Therapy. Two courses of anthracycline-based chemotherapy, either ADE or AD, was induction chemotherapy course 1. ADE administration consisted of daunorubicin 50 mg/m^2 daily by 1-hour intravenous infusion on days 1, 3, and 5 [total of 3 doses], cytarabine 100 mg/m^2 every 12 hours by intravenous push on days 1–10 [total of 20 doses], and etoposide 100 mg/m^2 daily by 4-hour infusion on days 1–5 [total of 5 doses]. AD therapy consisted of daunorubicin and cytarabine. The second induction chemotherapy course was identical to the first course except that cytarabine was given for 8 days.

Postremission Therapy. Two courses of high-dose cytarabine-based chemotherapy (cytarabine 3000 mg/m^2 during 4 hours, given every 12 hours on days 1, 3, and 5 [total 6 doses]) were used as consolidation therapy. Patients showing a partial remission after induction chemotherapy received Fla-Ida (fludarabine 30 mg/m^2 daily on days 1–5, cytarabine 2000 mg/m^2 daily on days 1–5, and idarubicin 10 mg/m^2 by 1-hour intravenous infusion on days 4, 5, and 6) as consolidation therapy.

Hematopoietic Stem Cell Transplantation. Patients with high-risk disease who had an HLA-matched sibling donor available underwent allogeneic hematopoietic stem cell transplantation. The conditioning regimen used consisted of busulfan, cyclophosphamide, and melphalan with methotrexate and cyclosporine for graft-versus-host disease prophylaxis.

Supportive Care. All patients were hospitalized for the initiation of induction chemotherapy. Tumor lysis prophylaxis with hyperhydration and allopurinol was commenced 24 hours before the start of chemotherapy and continued for at least 4 days. Intake, output, and electrolytes were monitored carefully.

All subsequent chemotherapy courses were given as inpatient. However, clinically stable patients were discharged after chemotherapy and admitted immediately in case of fever or any other problem. Patients

Figure. Overall survival (A) and Disease-free survival (B) between 2 chemotherapy groups.

AD, daunorubicin and cytarabine; ADE, daunorubicin and cytarabine with etoposide

not admitted in the hospital were reviewed at least twice weekly in outpatient clinics. No prophylactic antimicrobials and colony-stimulating factors were used during the neutropenic period. However, all cases of febrile neutropenia were treated as an inpatient with broad-spectrum intravenous antibiotics. Fever was defined as a single oral temperature of $>38^{\circ}\text{C}$ or 2 readings $>37.5^{\circ}\text{C}$ at least 2 hours apart. Neutropenia was defined as an absolute neutrophil count of <1000 cells/ μL . Febrile patients with absolute neutrophil count <1000 cells/ μL were treated with a combination of piperacillin-tazobactam and amikacin as per the hospital guidelines, based on recommendations of microbiology and the Infectious Diseases Society of America. Vancomycin or teicoplanin was added if a central venous line infection was suspected. Meropenem replaced piperacillin-tazobactam if fever continued after 48 hours. Amphotericin B was added empirically if fever continued beyond 96 hours.

Blood and blood products transfusion was given on an as needed basis. Hemoglobin transfusion threshold was 8.0 g/dL. Thresholds for platelet transfusion were 10×10^9 cells/L for asymptomatic and 20×10^9 /L for febrile patients. Treatment-related mortality (TRM) was defined as death occurring after start of chemotherapy due to chemotoxicity, in the absence of progressive cancer.

Statistical Analysis. The t test and χ^2 tests were used for comparison between continuous and categorical variables. Disease-free survival (DFS) was defined as the time from the achievement of CR until relapse. Overall survival (OS) was defined as the time from the date of diagnosis until the last follow-up or death from

any cause. The DFS and OS were estimated by using the Kaplan-Meier method, and log-rank tests (Mantel-Cox) were used to compare survival differences. All statistical analyses were performed using the SPSS 23.0, and p value < 0.05 was considered statistically significant. The Figure shows the DFS and OS between the 2 chemotherapy groups.

Results

Data of 186 cases of pediatric AML, including 117 males (62.9%) and 69 females (37.1%), were analyzed. There were 105 patients (56.5%) in the ADE group, and 81 patients (43.5%) in the AD group. The median ages were 6.08 ± 3.65 and 5.98 ± 3.45 years ($p = 0.877$) in ADE and AD groups, respectively. Demographics, initial presentation blood counts, and AML subtypes were almost equal in both groups (Table 1).

There were more complications during induction chemotherapy in the ADE group, but this difference was not significant. The incidence of neutropenic fever was 98.1% in the ADE and 93.8% in the AD group ($p = 0.109$). The incidence of fungal infection was 7.5% in the ADE and 3.8% in the AD group ($p = 0.233$). Treatment-related mortality during the first chemotherapy course was 22.0%. The TRM was greater, albeit not significantly, in the ADE group (23.8%) than in the AD group (19.8%; $p = 0.508$). Time of blood count recovery and start of second chemotherapy course were similar between the ADE and AD groups: 34.08 ± 9.74 and 33.95 ± 15.43 days, respectively ($p = 0.512$). After the first course of chemotherapy, 145 patients underwent BM aspiration to document remission status. Response to chemotherapy was almost identical in the 2 groups. The CR

Table 1. Patient Characteristics and Chemotherapy Response (N = 186)*

Variable	ADE	AD	Total	p value
Total No.	105 (56.5)	81 (43.5)	186 (100)	
Age, yr, mean $\pm$ SD	6.08 $\pm$ 3.65	5.98 $\pm$ 3.45	6.04 $\pm$ 3.55	0.877
Age groups				0.250
<5 yr	40 (38.1)	39 (48.1)		
5–10 yr	46 (43.8)	26 (32.1)		
10–15 yr	19 (18.1)	16 (19.8)		
Sex				0.082
Male	61 (58.1)	56 (69.1)	117 (62.9)	
Female	44 (41.9)	25 (30.9)	69 (37.1)	
WBC count, $\times 10^9/L$, mean $\pm$ SD	56.16 $\pm$ 71.59	51.56 $\pm$ 63.47	54.15 $\pm$ 68.04	0.433
Hemoglobin, g/dL, mean $\pm$ SD	7.44 $\pm$ 2.76	7.62 $\pm$ 2.15	7.52 $\pm$ 2.51	0.029
Platelets, $\times 10^9/L$, mean $\pm$ SD	51.54 $\pm$ 71.76	52.71 $\pm$ 55.70	52.05 $\pm$ 65.09	0.449
WBC count $>50 \times 10^9/L$	38 (36.2)	29 (35.8)	67 (36.0)	0.540
WBC count $<50 \times 10^9/L$	67 (63.8)	52 (64.2)	119 (64.0)	0.433
French–American–British classification				0.189
AML-M0	10 (9.5)	6 (7.4)	16 (8.6)	
AML-M1	13 (12.4)	4 (4.9)	17 (9.1)	
AML-M2	42 (40.0)	50 (61.7)	92 (49.5)	
AML-M4	15 (14.3)	8 (9.9)	23 (12.4)	
AML-M5	6 (5.7)	3 (3.7)	9 (4.8)	
AML-M6	3 (2.9)	1 (1.2)	4 (2.2)	
AML-M7	2 (1.9)	2 (2.5)	4 (2.2)	
AML-NOS	14 (13.3)	7 (8.6)	21 (11.3)	
Total	105	81	186	
Status after first induction chemotherapy (n = 186)				0.767
Treatment-related mortality	25 (23.8)	16 (19.8)	41 (22.0)	
Complete remission	63 (60.0)	52 (64.2)	115 (61.8)	
Partial remission	12 (11.4)	9 (11.1)	21 (11.3)	
Resistant/refractory disease	5 (4.8)	4 (4.9)	9 (4.8)	
Total No.	105 (100)	81 (100)	186 (100)	
Status after second induction chemotherapy (n = 135)				0.714
Treatment-related mortality	5 (6.8)	2 (3.2)	7 (5.2)	
Complete remission	63 (86.3)	57 (91.9)	120 (88.9)	
Partial remission	4 (5.5)	2 (3.2)	6 (4.4)	
Resistant/refractory disease	1 (1.4)	1 (1.6)	2 (1.5)	
Total No.	73 (100)	62 (100)	135 (100)	

AD, daunorubicin and cytarabine; ADE, daunorubicin and cytarabine with etoposide; AML, acute myeloid leukemia; WBC, white blood cell

* All values are n (%) unless otherwise indicated

rates were 78.8% and 80.0% in the ADE and AD groups, respectively ($p = 0.980$; Table 2).

Three patients having resistant disease did not get any further treatment. Second chemotherapy was given to 142 patients and included 73 (51.4%) in the

ADE group, 62 (43.7%) in the AD group, and 6 (4.9%) in the Fla-Ida group. For this study, the Fla-Ida group was excluded and the data for 135 patients undergoing ADE (73 cases) and AD (62 cases) were analyzed. During the second chemotherapy, 7 patients (5.2%),

Table 2. Response to Chemotherapy (N = 186)*

Variable	ADE	AD	Total	p value
First chemotherapy course				
Total No.	105 (56.5)	81 (43.5)	186 (100)	
Treatment-related mortality	25 (23.8)	16 (19.8)	41 (22.0)	0.508
Bone marrow examination status (n = 145)				
Complete remission	63 (78.8)	52 (80.0)	115 (79.3)	0.980
Partial remission	12 (15.0)	9 (13.8)	21 (14.5)	
Resistant/refractory disease	5 (6.3)	4 (6.2)	9 (6.2)	
Total No.	80 (100)	65 (100)	145 (100)	
Second chemotherapy course				
Total No.	73 (54.1)	62 (45.9)	135 (100)	
Treatment-related mortality	5 (6.9)	2 (3.6)	7 (5.5)	0.336
Bone marrow examination status (n = 128)				
Complete remission	63 (92.6)	57 (95.0)	120 (93.8)	0.791
Partial remission	4 (5.9)	2 (3.3)	6 (4.7)	
Resistant/refractory disease	1 (1.5)	1 (1.7)	2 (1.6)	
Total No.	68 (100)	60 (100)	128 (100)	

AD, daunorubicin and cytarabine; ADE, daunorubicin and cytarabine with etoposide

* All values are n (%)

including 5 (6.8%) in the ADE group and 2 (3.2%) in the AD group, died. Again, TRM during the second chemotherapy course was higher, albeit not significantly, in the ADE group than in the AD group (6.9% vs 3.6%, respectively; $p = 0.336$). A total of 128 patients who survived the second chemotherapy course had BM aspiration to document remission status. Response to chemotherapy was identical in both groups. Complete remission rates were 92.6% and 95.0% in the ADE and AD groups, respectively ($p = 0.791$; Table 2).

Two patients having resistant disease did not get any further treatment. A total of 126 patients, including 68 (54%) in the ADE group and 58 (46%) in the AD group, had a third course of chemotherapy. Three patients, including 1 in the ADE group and 2 in the AD group, died in the third course of chemotherapy. A total of 123 patients—67 (54.5%) in the ADE and 56 (45.5%) in the AD group—had a fourth chemotherapy treatment. There was no TRM in the last chemotherapy ($p = 0.079$), and DFS was 27.6% and 48.1% in the ADE and AD groups ($p = 0.056$), respectively. However, follow-up was significantly longer in the ADE group, with a mean of 687.03 ± 756.41 days vs 452.72 ± 441.59 days in the AD group ($p < 0.014$).

Discussion

The treatment of pediatric AML is divided into 2 phases, comprising induction and postremission consolidation. The goal of induction chemotherapy is to achieve complete morphologic remission, and

consolidation aims to reduce the risk of relapse.^{7–9} The outcome of AML in children improved in the last 20 years despite no major change in chemotherapy medications.¹⁰ The combination of daunorubicin and cytarabine has been the backbone of induction chemotherapy in both pediatric and adult AMLs since the 1970s, and is still the mainstay of induction therapy.^{4,6,11} Etoposide is a semisynthetic podophyllotoxin with anti-leukemic activity. It has a mechanism of action different from that of cytarabine and daunorubicin and is used in combination with these 2 agents. Its efficacy in the treatment of AML has been documented by various investigators.^{12–16}

In the present study, ADE and AD were compared to see any advantage of incorporating etoposide in the induction chemotherapy for pediatric AML treatment. However, no advantage of etoposide was documented. There were more episodes of neutropenic fever in the etoposide group. Treatment-related mortality was higher, albeit not significantly, in the ADE group (23.8%) than in the AD group (19.8%). Moreover, etoposide did not improve the remission rate. Complete morphologic remission rate was 78.8% with etoposide and 80.0% without etoposide. Several other publications have reported no benefit of etoposide in AML treatment. In the MRC AML15 trial, no advantage in rate and durability of response was documented with the addition of etoposide to daunorubicin and cytarabine. Overall remission rates were similar for the AD and ADE groups (84% vs 86%; $p = 0.14$). Patients had a higher rate of

death and CR resulting in similar overall survival with and without etoposide.^{6,17} Anderson et al¹⁶ conducted a phase 3 randomized clinical trial to assess induction outcome with daunorubicin and cytarabine versus mitoxantrone and etoposide. However, the study was closed early after the results of the interim analysis showed no improvement in CR rate and OS. The study concluded that the use of etoposide instead of cytarabine might have been the reason for the potentially worse outcome. Similarly, Miyawaki et al¹⁸ reported no advantage of the addition of etoposide to the induction therapy of AML in adult patients.

In the present study, the rate of complications, such as neutropenic fever and TRM, was higher in the etoposide group. This means more days of hospital stay and use of broad-spectrum antibiotics and antifungal therapy, resulting in an additional financial burden for the family and the hospital. In LMICs like Pakistan it is very difficult to afford the cost of such expensive treatments. Moreover, the addition of etoposide to induction treatment further increases the treatment cost without any advantage in the remission rate.

In the present study, induction therapy with etoposide also did not provide any survival advantage. Rather, it resulted in decreased OS and DFS, although this difference was not statistically significant. Relapse is a major challenge in the treatment of AML and is reported in 21% to 40% of cases.^{10,19} Although the etoposide group had delayed relapse, the relapse rate was higher in this group. The mean duration between the end of treatment and relapse was 244.04 days in the ADE and 191.41 days in the AD group ($p = 0.186$), and the relapse rate was 24.7% in the AD group and 41.0% in the ADE group. Similar results of there being no advantage in relapse-free survival with etoposide are reported by other publications.^{6,16}

The strength of the present study is that it was conducted with a quite significant number of pediatric AML patients from a LMIC. The weakness is that it is not a randomized control study. It is recommended that a randomized controlled trial be done for induction chemotherapy with and without etoposide in pediatric AML.

Conclusions

Etoposide in the induction treatment of pediatric AML is associated with increased episodes of bacterial and fungal infections and high TRM. Moreover, it does not offer any survival benefit. In LMICs like Pakistan it should not be used in the induction treatment protocol. Daunorubicin and cytarabine as used in adult treatment protocols are good enough induction chemotherapy agents for pediatric AML.

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Ethical Approval and Informed Consent Given the nature of this study, the project was exempt from institution review board/ethics committee review and HIPAA authorization, assent, and parental permission were not required.

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