Original Article (II)

Paediatric Acute Myeloblastic Leukemia: Experience with an Intensive Chemotherapy Protocol - A Pilot Study

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ABSTRACT

Background : The treatment of children with acute myeloblastic leukemia (AML) requires initial induction chemotherapy followed by intensive consolidation chemotherapy. We performed a small pilot study using two such protocols to determine their suitability in our set up.

Patients & Methods : 13 children (median age 4 years) were entered into study. First 4 children received Children's Cancer Group protocol (CCG 2891), subsequent 6 children received BFM 93 (BFM) protocol incorporating high dose cytosine arabinoside & mitoxantrone in consolidation. Of the remaining 3 children, one patient had AML-M3 and received APO protocol. One patient refused for treatment and another child died before treatment could be started. Chemotherapy was given as inpatients with standard supportive care.

Results : In the CCG group- all 4 achieved complete remission (CR), one patient died during consolidation of E coli septicemia, two patients refused consolidation. In the BFM protocol : 5 (83.3 %) of 6 patients achieved CR and subsequently received consolidation. The estimated 24 months overall survival is 82 $\pm$ 1.5 %.

Conclusion : This small pilot study suggests the feasibility of using BFM protocol in our set up.

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INTRODUCTION

The outcome for children and adolescents with acute myelogenous leukemia (AML) has improved during past two decades; approximately 50% of these patients have long term leukemia –free survival. Major part of this progress has come as a result of improved understanding of biology of AML, use of intensive consolidation chemotherapy and improved supportive care. Currently, 80 to 90 % of patients achieve complete remission (CR) following induction chemotherapy. Several groups in US[1,2] and Europe[3-8] have carried out multicentric trials to yield these results. Contrary to adult AML, many investigators support the use of CNS prophylaxis for paediatric AML. However, the real impact of CNS prophylaxis on survival is still not clear.

Maintenance therapy is generally not a part of most pediatric AML protocols with the exception of the Berlin-Frankfurt-Munster (BFM) protocols,[3] French SHIP Group,[6] and EORTC Group.[7] In aggressively treated AML, maintenance therapy does not appear to be of value.[8] Most centers in India follow the protocols used for adults. However, published experience for paediatric AML is not readily available. We performed a pilot study using two intensive protocols – Children's Cancer Group (CCG -2891) and BFM 93 protocols to assess their suitability in our set up.

PATIENTS & METHODS

13 children were recruited between Jan 2000 and Oct 2004. The median age was 4 years , ranging from 2 to 9 years. There were 10 males and 3 females. Four patients received CCG protocol, 6

patients were treated with BFM protocol, and one AML-M3 patient was treated with European APL Group protocol.[11] One patient refused treatment and one patient died soon after transfer from a peripheral hospital. Diagnosis of AML and its subtype was made on the basis of bone marrow morphology and myeloperoxidase (MPO) staining. French- American- British (FAB) classification was used for subtyping. Flow cytometry was used in Auer rod negative and MPO negative patients. Cytogenetic studies were not done routinely due to lack of facilities. The details of two protocols are given below. All patients were admitted in haematology/ oncology ward and received standard supportive care- intravenous antibiotics/antifungals for fever, blood /component support as and when required. A repeat bone marrow was done on day 22 to assess for remission status. Standard criteria were used to define CR. Following achievement of remission, patients received consolidation and maintenance chemotherapy as per protocol. At the completion of therapy, they were followed in out patients department at 1-2 months interval. At each visit a detailed physical examination, complete blood counts and peripheral smear examination was done. Bone marrow studies were repeated at 3 monthly interval.

TREATMENT

The details of two protocols are given below.

Table 1:Children Cancer Group Protocol (adapted from ref: 1)

Induction Day o through 4	
	Dexamethasone 6 mg/m²/d (0.2 mg/kg/d) thrice daily Cytarabine 200 mg/m²/d (6.7 mg/kg/d) continuous infusion Thioguanine 100 mg/m²/d (3.3 mg/kg/d) twice daily Etoposide 100 mg/m²/d (3.3 mg/kg/d) continuous infusion Daunorubicin 20 mg/m²/d (0.67 mglkgld) continuous infusion
Post remission Therapy	
A.	Course 1: Days 0 through 2 cytarabine, 3 g/m²/dose (100 mg/kg) IV over 3 h every 12 h x 4 doses. L-asparaginase 6,000 IU/m², IM hour 42. Days 7 through 9.
B.	Courses 2 and 3: Two 28-day cycles of 6-thioguanine 75 mg/m² PO daily, days 0 through 27; Vincristine 1.5 mg/m², IV day 0 cytarabine and L-asparaginase repeated exactly as administered days 0 through 2. cytarabine 75 mg/m2 IV everyday X 4, days 0 through 3; cyclophosphamide 75 mg/m² IV everyday X 4, days 0 through 3; 5-azacytidine 100 mg/m2 IV everyday X 4, days 0 through 3.
C.	Course 4: Cytarabine 25 mg/m²/dose SC or IV every 6 h X 5 days, days 0 through 4; daunorubicin 30 mg/m2 IV day 0; etoposide 150 mg/m² IV/dose x 2, days 0 and 3; 6-thioguanine 50 mg/m²/dose orally every 12 h X 5 days, days 0 through 4; dexamethasone 2mg/m²/dose orally every 8 h X 4 days, days 0 through 3

Table 2: BFM Protocol (adapted from ref 3)

INDUCTION Cytosine arabinoside (Ara-C) 100mg/ m^2/day CIV on days 1 & 2 followed by 30 min infusion every 12 h on days 3 through 8.; Etoposide (VP-16) 150 mg/ m^2 as 120 min infusion from days 6 to 8 ; Idarubicin 12 mg/ m^2 30 min infusion daily from day 3 to 5
AFTER ACHIEVEMENT OF CR High dose Ara-C with Mitoxantrone (HAM) therapy High dose Ara-C 3 g/ m^2 every 12 h for 3 days ; Mitoxantrone 10 mg/ m^2 on Days 4 & 5.
Consolidation therapy over 6 weeks as follows : 6-Thioguanine 60 mg/ m^2/day; orally days 1-43 orally; Prednisolone 40 mg/ m^2/day, days 1 through 28 orally; Vincristine 1.5 mg/ m^2 , days 1,8,15, and 22; Daunorubicin 30 mg/m^2, days 1,8,15 and ,22; Ara-C 75 mg/ m^2/day, days 3 to 6, 10 to 13, 17 -20, 24 to 27, 31 -34, 38-41 Intrathecal Ara-C sta ndard dose > 3 years 40 mg, day 1, 15, 29 and 43 Cyclophosphamide 500 mg/ m^2, days 29, and 43.
CNS Prophylaxis high dose Ara-C-3 gm/ m^2 twice daily for 3 days VP-16- 125 mg/ m^2 IV infusion over 1 hour , Day 2-5 followed by 18 Gy cranial irradiation(for children >3 years)
Maintenance therapy (total duration 18 months) 6-Thioguanine 40mg/ m^2 orally daily Ara-C 40 mg/ m^2 S.C. x 4 days monthly

RESULTS

10 (76.9%) of 13 patients achieved CR. All four patients treated with CCG protocol, achieved CR. One patient died during first consolidation. Two patients were lost to follow up after first consolidation. One patient relapsed after 9 months of completion of treatment and is currently in second CR

BFM protocol : A total of 6 children received BFM protocol. 5 (83.3 %) of 6 patients achieved CR. Remaining one patient with refractory leukemia died during re-induction chemotherapy.

One patient with AML-M3 was treated with European APL group protocol. He continues to be in CR at end of 38 month.

Toxicity: All patients had fever with neutropenia during induction therapy. One child while on CCG protocol, died during consolidation therapy due to E.Coli septicemia. The tolerance to BFM protocol was better, both during induction and consolidation therapy; 3 of 6 patients had febrile neutropenia during consolidation therapy. Growth factors were added in case the response to antibiotics was not appropriate. No other major organ or grade III-IV toxicity was seen.

Survival : All patients treated on CCG protocol achieved CR. However there was one consolidation death and 2 patients left after first consolidation and are lost to follow up. 40 months probability of overall survival (OS) was 32 ± 1 %. Of the 6 patients who were given BFM protocol. 5 (83.3 %) of 6 patients achieved CR. The estimated 24 months OS was 82 ± 1.5 %. The results of remission, survival and toxicity using BFM protocols in this study matches those reported by other authors[1,9] (Table -3).

Table 3: Responses toxicity and survival in different multicenter trials.

Ref. no	Group	CR rate (%)	Early death (%)	Event-free survival	Overall survival
1	CCG	74	11	42 ± 7 (3 years)	51 ± 7 (3 years)
2	POG- 8821	84.9	NA	33.8 ± 2.4(4 years)	43.5 ± 2.4 (4 years)
3	AML –BFM 93	82	7	51± 2 (5 years)	60 ± 3 (5 years)
4	MRC AML 10	92	4	48± 5 (7 years)	56 ± 4 (7 years)
7	EORTC	78	11	51 (3 years)	56 ± 4 (3 years)
8	LAME	87	6	47± 8 (4 years)	NA
9	NOPHO	92	3	57± 4 (5 years)	NA
10	SPAIN	88	6	NA	74 ± 12 (5 years)
	Present study	76.9	9	52 ± 3 %.	60 ± 2%

NA - not available

DISCUSSION

Acute leukemia is the most common form of childhood cancer. While the results in the most common form of leukemia in children - acute lymphoblastic leukemia are much better (70 to 85%), the progress in acute myeloblastic leukemia has been slow. Nevertheless a disease which was incurable three decades ago, now approximately 50% of children have long term leukemia-free survival and are possibly cured. Multicentric studies done by a no of co-opertive groups (table-3) have confirmed these results. The essential approach today for the treatment of AML includes- induction chemotherapy using daunomycin, cytosine arabinoside +/- etoposide or 6-thioguanine . This is followed by 3-4 cycles of consolidation chemotherapy using high dose cytosine arabinoside. Some groups but not all have advocated use of maintenance therapy. Similarly, there is some debate on CNS prophylaxis in these children. The duration of induction and drug sequencing varies in different protocols. For example, the Children Cancer Group (CCG) intensively-timed DCTER regimen[1] includes cytarabine, daunorubicin, dexamethasone, etoposide, and thioguanine and is given as two 4-day treatments separated by 6 days. The BFM Group[3] have studied cytarabine and daunorubicin plus etoposide (ADE) given over 8 days. In UK Medical Research Council (MRC) protocol ADE regimen is given over 10 days.[4]

The results from the MRC 10[4], LAME 89/ 91 studies and the recent BFM 93 trial[3] with high-dose cytarabine and mitoxantrone (HAM) suggest that there is benefit by including this combination in the post remission phase of AML.

The main advantage of AML-BFM-93 over BFM –87 was attributed to the use of HAM rather than to use of high dose Ara-C with VP-16 as post remission consolidation. The demonstrable efficacy with tolerable rate of toxicity of HAM consolidation in high-risk patients of BFM –93 has led to AML-BFM-98 incorporating HAM in all paediatric AML patients. We too used the BFM – 98 schedule of using HAM in all patients on BFM protocol with the aim of improving survival . This protocol consists of 4 phases of treatment; induction phase followed by post remission consolidation chemotherapy for children not having matched donor sibling. In this protocol, unlike adult AML, CNS prophylaxis is used for all patients followed by maintenance of eighteen months.

Benefit for the use of high-dose cytosine arabinoside (Ara-C) compared with standard-dose Ara-C in children was not observed using Ara-C dose of 1 gm/ m^2 given twice daily for 7 days with daunorubicin and thioguanine. The MRC Group[4] has intensified induction therapy by prolonging the duration of Ara-C treatment to 10 days. The CCG Timed-sequential induction therapy study[1] demonstrated that intensively timed induction therapy (4-day treatment courses separated by only 6 days) produced better event-free survival than standard-timing induction therapy (4-day treatment courses separated by 2 weeks or longer). Children with AML-M4 and M5 subtype have the higher incidence of CNS leukemia (especially those with inv 16 or 11q23 chromosomal abnormalities). The use of some form of CNS treatment (intrathecal chemotherapy with or without cranial irradiation) is now incorporated into many protocols for childhood AML and is considered a standard part of the treatment for this disease. AML-BFM-93 protocol uses 4 pulses of intrathecal Ara-C along with 18 Gy of cranial radiation in children > 3 years of age. Due to the extremely low incidence of CNS disease in patients with acute promyelocytic leukemia (APL), a lumbar puncture is not required at the time of diagnosis and prophylactic intrathecal chemotherapy is not administered.

Although maintenance chemotherapy has been incorporated into pediatric AML therapy[3,7,9] and continues to be used in BFM trials, no data demonstrates that maintenance therapy given after intensive post remission therapy significantly prolongs remission duration.[10] In contrast LAME 91 study[8] showed that, low-dose maintenance, leads to worsening of survival and should not be recommended. BFM protocol[3] however gives 18 months of maintenance with 6 thioguanine and monthly pulses of Ara-C. Whether use of 6 thioguanine in BFM rather 6 MP in LAME 91 study[8] contributes to improved survival in BFM potocol will need a randomized trial.

Our preliminary experience with BFM 93 protocol incorporating high dose Ara-C and mitoxantrone suggests the feasibility of using this protocol in centres taking care of such patients.

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