

Management of acute myeloid leukaemia - 5 years experience at Armed Forces Bone Marrow Transplant Centre, Rawalpindi

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Abstract

Objective: To evaluate the outcome in denovo AML patients treated with different remission induction and consolidation chemotherapy regimens in our population.

Methods: A retrospective study on acute myeloid leukaemia (AML) patients was carried out at Armed Forces Bone Marrow Transplant Centre Rawalpindi Pakistan between July 2001 and June 2006. During 5 years period 46 patients received treatment for AML at our centre. Twenty nine patients were males and 17 were females. Median age of patients was 21 years (range: 7 -56 years). These 46 patients were categorized into two groups on the basis of type of leukaemia and chemotherapy given. In group-I 40 patients (group Ia: 23 patients of M1-M6, less M3 group Ib: 17 patients of AML M3) received anthracycline and cytarabin based chemotherapy. In group- II, six patients (AML- M3) received all trans retinoic acid (ATRA) based chemotherapy.

Results: In group Ia, out of 23 patients, 14 patients (60.8%) achieved complete remission (CR) after remission induction chemotherapy, 10 patients remained in CR after 3rd and 4th consolidation. Eleven patients died and five patients relapsed during treatment and follow up. In this group overall CR, relapse rate (RR) and mortality was 30.4% (7/23), 21.7% (5/23) & 48% (11/23) respectively. In group Ib out of 17 patients, 9 patients (53%) achieved CR after remission induction. Eleven patients died during treatment while one patient relapsed in this group. Overall CR, RR & mortality was 29.4% (5/17), 6% (1/17) & 55% (11/17) respectively. In group II all patients achieved CR (100%) after 1st course of chemotherapy. Two of these patients unfortunately died of uncontrolled sepsis during 1st consolidation, while remaining 4 patients 66.6% are on maintenance chemotherapy and are still in CR.

Conclusion: Overall CR, RR and mortality in all groups was 35% (16/46), 13% (6/46) and 52% (24/46) respectively at a median follow-up of 36 + 8 months. Survival in AML-M3 patients treated with ATRA based chemotherapy is significantly superior than anthracycline based chemotherapy (66.6% vs 29.4%). Infection and chemotherapy toxicity being major causes of mortality (JPMA 57:434:2007).

Introduction

Acute Myeloid Leukemia (AML) is a heterogeneous, invariably fatal disease if untreated.¹ About 70% of AML patients present with cytogenetic

abnormalities, however the percentage of known genetic alterations is much lower.² Prognostic factors predicting treatment outcome include age, sex, performance status, white blood cell count, splenomegaly, presence or absence

of bleeding or infection, time to achieve CR and AML subtype.^{3,4}

Remission induction therapy in AML is the most difficult phase in the management of these patients.^{5,6} Current chemotherapy with advanced supportive care will enable 75% to 80% of AML patients to enter complete remission.⁷ Most patients with de novo AML achieve complete remission following induction therapy, however long term disease free survival is observed in only 25-50% of patients. The early mortality during remission induction phase has been reduced from the earlier figures of 20-30% to 10-15% in patients less than 60 years of age.^{8,9}

Acute promyelocytic leukemia (APL) accounts for 10-15% of denovo cases of AML in younger adults and is characterized by a reciprocal translocation that involves chromosomes 15 and 17. Remarkable progress has occurred in the treatment of patients with APL since the introduction of all-trans retinoic acid (ATRA). Targeted therapy with ATRA based chemotherapy results in an apparent cure in 70-80% of patients.¹⁰⁻¹² Both allogeneic and autologous stem cell transplantation (allo & auto SCT) are effective in AML but their role in APL is not clear given the excellent outcome with ATRA based chemotherapy.¹³

Post-remission therapy in AML remains problematic. Once remission is induced, further intensive treatment of patients with AML is essential to prevent relapse. Three options are available for younger patients: Allo SCT (from an HLA-matched related or unrelated donor), auto SCT, or intensive consolidation chemotherapy (ICC). Results of ICC in adults patients with AML are similar to allo SCT in first remission.^{14,15} However in children overall survival has been reported to be higher in allo SCT as compared to ICC and auto SCT.¹⁶ Extensive database analysis according to evidence based medicine (EBM) has highlighted the limitations observed in published studies concerning consolidation therapy in AML. These include emergence of genetics subgroups and biological heterogeneity of AML. New drugs targeting specific abnormalities could eventually become the cure of each specific subtypes with its peculiar biological, molecular and prognostic features.¹⁴

With this background, we are presenting our initial experience in the management of AML at Armed Forces Bone Marrow Transplant Centre (AFBMTTC) Rawalpindi over a period of 5 years. The main objective of the study is to assess the response to different remission induction and intensification regimens used in the management of acute myeloid leukemia and long term outcome in these patients.

Patients and Methods

This retrospective study was carried out at Armed

Forces Bone Marrow Transplant Centre, (AFBMTTC) Rawalpindi, Pakistan between July 2001 and June 2006. All patients with AML fulfilling the following eligibility criteria were included: all newly diagnosed cases of AML with an age less than 60 years and a good performance status.

The exclusion criteria were: patients older than 60 years of age, ECOG performance status > 2, multiple organ dysfunction with ALT more than twice the normal, creatinine more than normal, cardiac ejection fraction < 60%, pregnant and lactating females and patients having concurrent active malignancies

All patients were diagnosed and classified into AML subtypes on the basis of FAB classification. Initially cytogenetic analysis was not a routine practice in our hospital however for the last 2 years. It is being done in all newly diagnosed cases of AML now. AML patients were categorized in two groups, group I (Ia and Ib) and Group II and chemotherapy was planned.

Criteria for the assessment of complete remission (CR) status were based on bone marrow examination showing <5% blasts, done at day+20 post chemotherapy or when ANC>1.0x10⁹/L. Criteria for persistent disease were based on day+20 bone marrow examination findings; >20% blasts in a marrow having at least 20% cellularity. Minimal residual disease (MRD) status was assessed by fluorescent immunosorbant hybridization (FISH) / RT-PCR. Criteria for relapse status was > 20% blasts in the marrow after achieving complete remission.

Results

During this period of 5 years, a total of 53 newly diagnosed AML patients reported at AFBMTTC, Rawalpindi

Table 1. Patient characteristics.

Age (years)		
< 20 Years	:	8
21-40 Years	:	26
41-60 Years	:	12
Sex (Male/Female)	:	29/17
FAB Classification		
M1	:	4
M2	:	16
M3	:	23
M4	:	2
M5	:	1
Cytogenetics		
Normal Karyotype	:	5
t (8:21)	:	7
t (15:17)	:	14
Not done	:	20

Table 2.

A. Anthracycline / cytarabine based remission induction and consolidation chemotherapy in AML
Group Ia (n=23) and group Ib (n=17)

Induction

- Course 1: Cytosine arabinoside 100mg/m², 12 hourly, slow IV push day 1-10 (20doses)
 Daunorubicin 50mg/m², slow IV push on day 1,3 & 5 (3 doses)
 Etoposide 100mg/m², IV infusion over 1 hour, day 1-5 (5 doses)
 Consolidation
- Course 2: Cytosine arabinoside 100mg/m², 12 hourly, slow IV push day 1-8 (16 doses)
 Daunorubicin 50mg/m² slow IV push on day 1,3 & 5 (3 doses)
 Etoposide 100mg/m², IV infusion over 1 hour, day 1-5 (5 doses)
- Course 3: Idarubicin 10mg/m² slow IV push day 1,2,3 (3 doses)
 Cytosine arabinoside 100mg/m², IV infusion over 2 hours, 12 hourly day1-5 (10 doses)
 Etoposide 100mg/m², IV infusion over 01 hour, day 1-5 (5 doses)
- Course 4: Mitozantrone 10mg/m² slow IV push day 1-5 (5 doses)
 Cytosine arabinoside 1g/m² IV infusion over 02 hours 12 hourly, day 1-3 (6 doses)
- Course 5: Cytosine arabinoside 3g/m², IV infusion over 04 hours 12 hourly on day 1,3 & 5 (6 doses)

B. ATRA based remission induction, consolidation and maintenance Chemotherapy in APL
Group II (n=6)

Remission Induction

- Course 1: Idarubicin 12mg/m², I/V infusion over 30 mins on day 2,4,6 & 8 (4 doses)
 All trans retinoic Acid (ATRA) 45mg/m² till CR or day+90

Consolidation

- Course 2: Idarubicin 5mg/m²/d days 1-4 (4 doses) Cytosine arabinoside 1g/m² day 1-4 (4 doses)
 ATRA 45mg/m²/d PO days 1-15
- Course 3: Mitozantrone 10mg/m²/d, I/V Infusion over 30 mins day 1-5 (5 doses)
 Etoposide 100mg/m²/d, IV infusion Over 01 hour, 12 hours after Mitozantrone days 1-5, (5 doses)
- Course 4: Idarubicin 12mg/m²/d, I/V day-1 (1 dose)
 Cytosine arabinoside 150mg/m² IV 8 hourly on (Days 1-5) (15 doses)
 6-Thioguanine PO, 70mg/m²/8 hourly Days 1-5

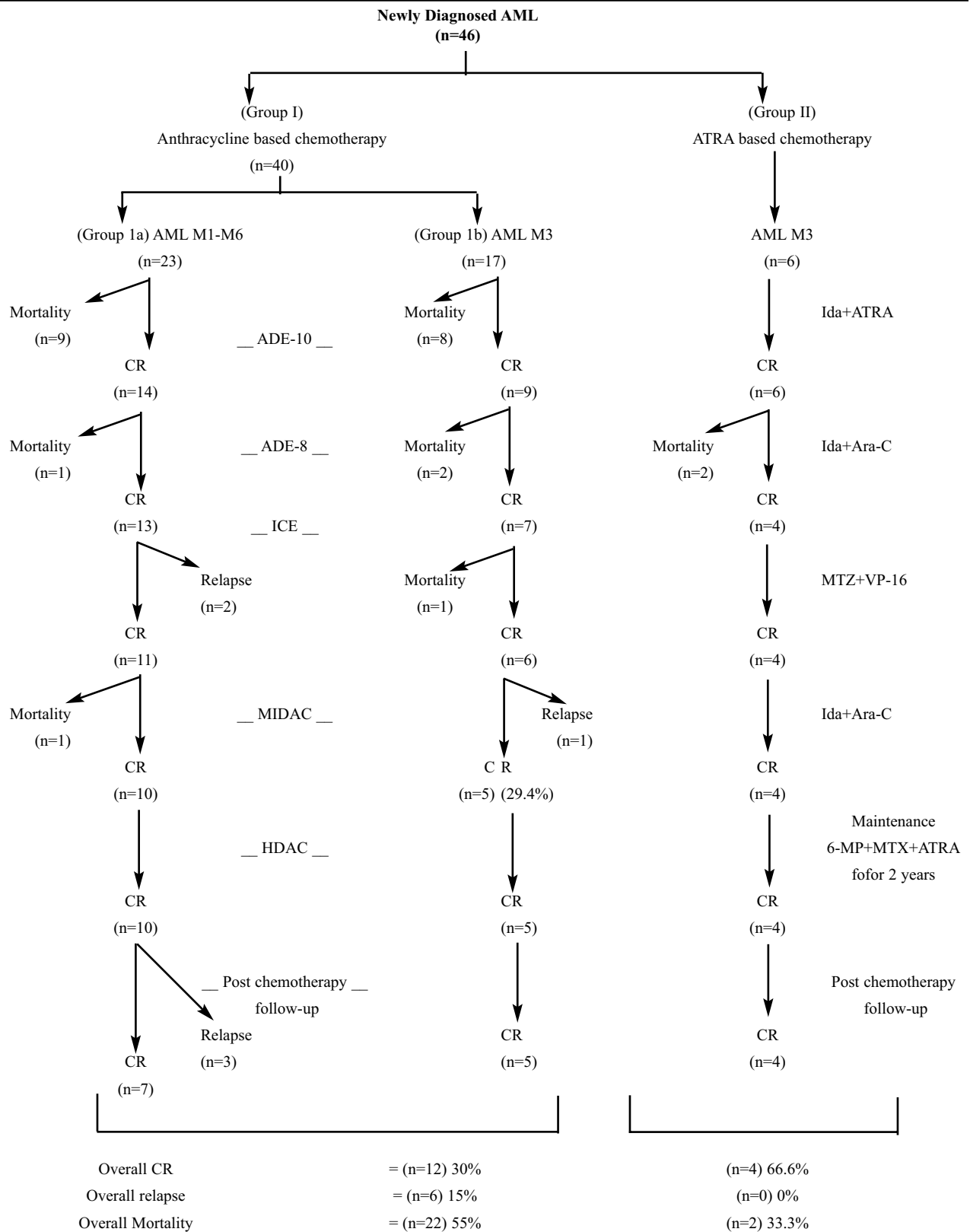
- Maintenance** (for 2 years) ATRA 45mg/m²/d for 15 days every 3 months
 Methotrexate 15mg/m², weekly P.O
 6-Mercaptopurine 50mg/m², daily PO

for management. Out of these 7 patients were lost to follow up during different stages of treatment, so these were excluded from the study. Of the remaining 46 patients included in study, 29 were male and 17 were female. Eight patients were < 20 years of age, 26 were between 21-40 years of age and 12 were between 41-60 years of age. Subtypes in these patients were, M1 (n=4), M2 (n= 16), M3 (n= 23), M4 (n=2) and M5 (n=1) as shown in Table 1. These 46 patients were divided into 2 groups: group I&II depending on subtype of leukaemia and type of

chemotherapy given. Group 1 was further subdivided into group Ia and Ib. Group Ia included 23 patients with AML M1-M6 less AML M3 and group Ib included 17 patients with AML M3. Group Ia and Ib received anthracycline based chemotherapy. Group II included 6 patients with AML-M3, who received ATRA based chemotherapy as shown in Table 2.

In-group Ia, 14 patients achieved CR after remission induction chemotherapy, 13 patients remained in CR after 1st consolidation, 11 patients maintained CR

Table 3. Outcome of patients in different sub-groups.



after 2nd consolidation and 10 patients remained in CR after 3rd and 4th consolidation. Eleven patients died during treatment. Five patients relapsed during treatment and follow up in this group. Two patients relapsed during consolidation chemotherapy. One patient relapsed within 6 months of completion of chemotherapy and two patients relapsed between 6 months and 1 year of chemotherapy. In group Ib out of 17 patients, 9 achieved CR after remission induction. Eleven patients died during treatment. One patient relapsed after 3rd consolidation. Five patients are still in CR and being followed-up. In group II out of six patients, all achieved CR after 1st course of chemotherapy. Two of these patients unfortunately died of uncontrolled sepsis during 1st consolidation, while remaining 4 patients are on maintenance chemotherapy and are still in CR.

A total of 46 patients received chemotherapy for acute myeloid leukemia. Of these 34.8% (16/46) in all groups are still in CR at the end of 5 years with 30% CR in group I (Ia = 30.4%, Ib = 29.4%) and 66.6% CR in group II patients. Overall outcome in different subgroups is shown in Table 3. Major causes of mortality were infections and chemotherapy induced toxicity. Infective causes of mortality were septicemia and DIC (11/24) and pneumonia (5/24) while non infective chemotherapy related causes of mortality were ARDS (3/24), acute renal failure (2/24), hepatotoxicity (2/24) and toxic ileus (1/24).

Discussion

Management of AML has two major goals: to induce complete haematological remission by cytoreductive chemotherapy and thereafter to prevent leukaemia relapse. In most of the centers induction regimens consist of anthracycline and cytarabine in conventional doses, producing a CR rate of 60-70%.¹⁷ In our study 63% (29/46) patients achieved CR after remission induction chemotherapy.

Post remission treatment is not uniform in AML patients. Three options are available once the patient achieves remission; intensive consolidation chemotherapy (ICC), allogeneic stem cell transplantation (allo SCT) and autologous stem cell transplantation (auto SCT).¹⁸ Allo SCT remains the treatment of choice for children/ adolescents as well as adults with AML in remission, when matched related donors are available. For all others there is no advantage of auto SCT over ICC.¹⁹ Wood WG et al²⁰ reported 60%, 48% and 53% disease free survival (DFS) in children after allo SCT, auto SCT and ICC respectively. Castaigne S et al²¹ reported 44%, 44% and 40% DFS in adults at 4 years after allo SCT, auto SCT and ICC respectively. Similarly Tracey A et al¹⁶ observed higher

DFS after allo SCT as compared to auto SCT (79-63%) in children in consecutive trials from Australia and New Zealand. Classical consolidation chemotherapy provides 8-40% 5 years disease free survival (DFS) in AML.²² In our study at the end of 5 years DFS was 34.8% after ICC at a median followup of 36 ± 8 months. None of our patients was subjected to either auto SCT or allo SCT.

Treatment of acute promyelocyte leukaemia (APL) with all-trans retinoic acid (ATRA) and Arsenic trioxide has become more rationale resulting in high cure and salvage rates.²³ Fenaux P et al²⁴ reported 80% event-free survival (EFS) in the ATRA group compared with 50-55% in anthracycline based chemotherapy arm.²³ In our study 66.6% DFS was observed in AML-M3 patients who received ATRA based chemotherapy as compared to 29% DFS in AML-M3 patients who received anthracycline based chemotherapy. ATRA was not easily available in Pakistan initially when we started treating APL patients but for the last 2 years it is freely available. Therefore now all newly diagnosed APL patients in our centres receive ATRA based chemotherapy. Although the number of patients who received ATRA based chemotherapy is small and at this stage it would not be realistic to predict the outcome and comparison of results in these two subgroups of APL. As the number of patients increase with longer duration of follow-up, outcome of APL with or without ATRA would be better analyzed. Better strategies to control and treat infections will further improve our results considerably in future.

Conclusion

Critical analysis of our results in AML show high mortality during remission induction. More than 50% of our patients died during induction and majority of these deaths were due to infections despite close liaison with microbiologists and targeted antimicrobial therapy as per our laid down protocol. In conclusion overall CR rate of 34.8% in AML at 5 years in our study is quite encouraging. However patients with AML-M3 who were treated with ATRA based chemotherapy achieved better disease free survival as compared to those AML-M3 who received anthracycline based chemotherapy. Better strategies to control and treat infection will further improve our results. Newer antifungals and antivirals are not easily available as these drugs are not registered in our country. The availability of these drugs at economical rates will be a break through in the management of infections in AML patients.

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