OUTCOME OF CHEMOTHERAPY IN NON ACUTE PROMYELOCYTIC ACUTE MYELOID LEUKAEMIA

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ABSTRACT

Objective: Retrospective analysis to evaluate overall response and outcome of various therapeutic regimens given in patients with non acute promyelocytic acute myeloid leukaemia (non APL AML).

Study Design: Retrospective study.

Place and Duration of Study: Armed Forces Bone Marrow Transplant centre/ National Institute of Blood and Marrow Transplant (AFBMTC/NIBMT), Rawalpindi.

Methodology: Patients of non APL AML managed at Armed Forces Bone Marrow Transplant Centre between Jul 2001 and Dec 2014 were evaluated. These patients included cases of denovo (n=103) and relapsed (n=18) AML cases. After baseline investigations bone marrow examination was carried out in all cases and cytogenetics and immunophenotyping in some cases. Informed written consent was taken before starting chemotherapy. The chemotherapy regimens used were D3A7, ADE, ICE, MAE, FLAG & FLAG-IDA and HiDAC. Majority of patients received induction with daunorubicin/cytarabine based chemotherapy. Post remission chemotherapy included either second course of D3A7/ADE combination or FLAG-Ida/ICE chemotherapy in relapsed AML followed by one to two courses of HiDAC (high dose cytarabine). Bone marrow examination was carried out after each course of chemotherapy to assess remission status.

Results: Total 121 cases were evaluated. Median age of patients was 28 years with 68% males and 32% females. Sixty four (53%) patients were of AML-M2 subtype. All 121 cases received induction chemotherapy including 103 denovo and 18 relapsed patients. Anthracycline based chemotherapy was given to majority of denovo cases (68%) while most of the relapsed AML patients received FLAG-Ida regimen. Hematological complete remission (CR) was achieved in 37% of denovo and 58% of relapsed patients after first course. Twenty nine (24%) patients failed to respond 11% had partial remission while 19 (15%) died within four weeks post induction and 9% discontinued the treatment.

Out of eighty patients who received second course of chemotherapy 60 (75%) achieved CR. Only 62 patients including 52 denovo and 10 relapsed cases completed four courses of chemotherapy and were followed for a period of one to five years after completion of treatment. Out of these 62 patients 31 (50%) achieved CR, six of these 31 subsequently relapsed and two are alive on palliation. Overall and disease free survival in patients who completed chemotherapy was 43% and 40% respectively.

Conclusion: A significant number of patients with AML can be saved provided proper risk adapted chemotherapy is given. Standard induction with daunorubicin/cytarabine chemotherapy followed by two to three courses of high dose cytarabine is associated with overall and disease free survival in a significant proportion of cases.

Keywords: Acute myeloid leukemia, Complete remission, Induction chemotherapy.

INTRODUCTION

Acute myeloid leukemia (AML) is characterized by clonal proliferation of immature hematopoietic precursors replacing normal bone marrow elements and resulting in anemia, neutropenia and thrombocytopenia[1]. Most of the patients have an acute onset and present with infection or bleeding within few weeks while older patients may have slowly progressive disease. Incidence of AML is high in Australia, U.S and Western Europe[2]. Overall incidence in U.S is about 3-4 cases per 100,000 per year[3]. with majority of cases occurring at 60 years of age or older[4]. According to U.S data on incidence of AML from 2001 to 2003, 1.8 per 100,000 patients were <65 years of

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age whereas 17 per 100,000 patients were 0.65 years of age[5]. Male predominance in AML has been reported in many epidemiological studies[6]. AML with myelodysplasia related changes is more common in males and this is due to 70% higher incidence of MDS in males than females[7].

Examining a blood and bone marrow aspirate films remains the most important early tool for the initial diagnosis of acute leukaemia followed by immunophenotyping in selected cases, cytogenetics, molecular genetics and genome wide studies for complete diagnostic work up and risk stratification[8]. Increasing age, poor performance status, high counts, poor risk cytogenetic and molecular genetics are features that adversely affect the outcome of patients[9,10].

Treatment of AML remains a challenge for haematologists and Oncologists. There is about 50% to 70% of complete remission (CR) rate in adults with cytarabine and anthracycline based regimens[11,12]. Anthracycline (daunorubicin 45-60 mg/m^2, or idarubicin, 10-12 mg/m^2 for three days and 100-200 mg/m^2 of cytarabine for seven days is most widely used standard induction regimen[13,14]. High dose cytarabine (HiDAC, 3g/m^2 12 hourly on days 1, 3 and 5), autologous stem cell transplant and allogeneic atem cell transplantation are various post remission therapeutic strategies[15-18]. HiDAC alone has proved to be superior to prolonged intensive consolidation or multiagent chemotherapeutic regimens[19-20]. This retrospectivestudy is designed to evaluate the overall response and outcome in AML patients who had received treatment in our hospital in last 12 years.

METHODOLOGY

This is retrospective analysis of 121 cosecutive non acute promyelocytic AML (non APL AML) patients who reported to Armed Forces Bone Marrow Transplant Centre, Rawalpindi, from July 2001 to December 2014. Non probability consecutive sampling was used. Patients with previous history of chemotherapy, secondary AML and patients with early deaths were not included in the study. All patients had bone marrow examination to confirm the diagnosis. Initial diagnosis was made on morphology, cytochemistry and immuno-phenotyping in selected cases. Conventional cytogenetics, FISH and molecular genetics were carried out in few but not all patients. Complete risk stratification was not possible due to non availability of the facility before 2005, financial constraints and culture failure.

Informed written consent was taken from all patients and parents of paediatric age group. Standard induction therapy comprising of an anthracycline (daunoblastina 45-60 mg/m^2, or idarubicin 10-12 mg/m^2) 3 days and 7 days of cytarabine (100-200 mg/m^2 continuously or twice daily intravenously) were given to majority of our patients. Other chemotherapeutic regimens that have been used during induction were ADE (cytarabine, daunorubicin, etoposide) and FLAG-Ida (fludarabine, cytarabine, idarubicin) in relapsed AML. Post remission chemotherapy (consolidation/reinduction) included two or three courses of HiDAC (cytarabine 3g/m^2, 12 hourly, days 1, 3, 5) ADE, M5E5 and FLAG-Ida.

Prophylactic antimicrobials (oral ciprofloxacin/moxifloxacin and oral fluconazole) were used in neutropenic patients as per hospital policy and prevailing infectious organisms. Special emphasis was given on personal hygiene, oral care and proper and critically supervised hand washing practices for patient's attendants and staff members. All febrile episodes were treated using intravenous piperacillin-tazobactam and amikacin with or without tiecoplanin as first line antibiotics. Amphotericin B was added to antibiotic regimen if fever persisted for more than 48 to 72 hours on first line antibiotics. Prophylactic platelet transfusion threshold was <10 x10^9/l and <20 x10^9/l in case of fever and haemoglobin was maintained above 8 g/dl.

Bone marrow examination was done after each course of chemotherapy to assess remission status. Response criteria used to label the patient in complete remission was, bone marrow blasts <5%, absence of extramedullary disease, absolute neutrophil count >1.0 x 10^9/l, platelet count >80 x

10^9/l and red cell transfusion independency. Frequency and percentage were calculated.

Statistical calculations were done using Statistical Package for Social Sciences (SPSS) version 17.0 (Chicago, Illinois, USA). Overall survival (OS) was calculated in all patients who completed all four courses of chemotherapy and were alive on date of last evaluation while disease free survival (DFS) was survival in the absence of disease or death.

RESULTS

Total of 128 patients of non APL AML reported at AFBMTC. Two patients of secondary AML, two relapsed cases for allogeneic bone marrow transplant and three early deaths were excluded from the study. Thus 121 cases were analysed for this study. The pretreatment characteristics of all these patients are listed in table-I. The mean age was 28 ± 2.05 years with a range of 8 to 57 years, 68% were males and 32% females. Based on morphology, cytochemistry and immunopheno typing in selected cases 53% cases were diagnosed as FAB AML-M2 subtype (table-I). Cytogenetic analysis was performed on pretreatment samples of only 35 patients (29%). Bone marrow culture failure was reported in 14 samples, therefore cytogenetic reports of only 21 (17%) patients are available including 18 (15%) patients of FAB AML-M2 (table-I).

All 121 patients received first course of chemotherapy including 103 de novo and 18 relapsed cases. Majority of patients received anthracycline based chemotherapy including 83 de novo and 18 relapsed cases of AML. CR was achieved in 49 (41%) of the 121 patients. Twenty nine patients (24%) failed to respond (NR), 13 (11%) had partial remission (PR) while 19 (15%) patients died post induction and 11 (9%) discontinued the treatment due to financial constraints and prolonged cytopenias.

Table-I: Patient and disease characteristics (n=121).

Characteristics	Number (%)
Age (years)	
1-20	36 (30)
21-40	66 (54)
41-60	19 (16)
Gender	
Male/female	82/39
Denovo AML	103 (85)
Relapsed AML	18 (15)
FAB Subtypes	
Mo	04 (3.3)
M1	16 (13)
M1R*	3 (2.4)
M2	49 (40)
M2R*	15 (12)
M4	20 (16.5)
M5	08 (6.6)
M6	04 (3.3)
M7	02 (1.6)
Haematologic values Median (range)	
Haemoglobin Level (g/dL)	8.4 (3.5-12.8)
WBC count (x10^3/ul)	19 (0.6-268)
Platelet count (x10^3/ul)	30 (0-531)
Cytogenetic Findings (n=35) Number	
Culture failure	14 (40)
Normal	11 (31)
T (8; 21)	04 (11.4)
Complex cytogenetics**	05 (14.3)
Trisomy 8	01 (2.9)

***Complex (>3 chromosomal abnormalities), *Relapsed AML*

Table-II: Patients' response to 2 courses of Induction chemotherapy (n=80).

Chemotherapy regimens	Number	CR	NR	PR	Death	Lost to follow
ADE/D3A7 ± HiDAC	24	20	2	-	1	1
ADE-2	18	16	-	1	-	1
D3A7-2	22	15	4	1	1	1
FLAG-Ida	13	7	5	-	1	-
Others (M5E5, ICE)	3	2	-	-	1	-
Total	80	60 (75%)	11 (13.75%)	2 (2.5%)	4 (5%)	3 (3.75%)

Eighty patients including those who were in PR (partial remission) after first course and those who were not in remission were subjected to second course of induction chemotherapy. Out of these 80 cases, Sixty patients (75%) achieved CR. Various chemotherapeutic regimens and patient's response following two courses of chemotherapy is shown in table-II.

Only 62 patients including 52 denovo and 10 relapsed cases completed four courses of chemotherapy and were followed for a period of one to five years after completion of treatment. Out of these 62 patients 31 (50%) achieved CR, four of these 31 subsequently relapsed and three are alive on palliation. Post remission courses given for consolidation in these 62 patients and their response is shown in table-III. Majority of patients experienced grade 3 or 4 myelosuppression after each intensification requiring aggressive blood component support and broad spectrum antimicrobials for neutropenic fever.

Table-III: Consolidation chemotherapy (n=62).

Chemotherapy regimens	CR, n (%)	Relapsed, n (%)	Death, n (%)	Lost to follow, n (%)
Denovo (n=52)				
HiDAC (n=31)				
Others (n=21)	19 (61)	2 (6)	10 (32)	-
ADE, ICE, MIDAC (n=10)	4 (19)	-	13 (62)	4 (19)
ADE, HIDAC (n=8)				
FLAG-Ida (n=3)				
Relapsed (n=10)	1 (16.7)	1 (16.7)	4 (66.7)	-
HiDAC (n=6)	3 (75)	-	1 (25)	-
FLAG-Ida (n=4)				

DISCUSSION

Management of AML is a challenge for hematologists. Most of the patients, approximately 50 to 65% achieve CR after one or two courses of induction chemotherapy, majority relapse within two years[21,22]. Management has two goals: to induce remission and to prevent relapse. Standard induction regimen consists of anthracycline and cytarabine in conventional doses[23]. We have evaluated outcome and response in our AML patients to various chemotherapeutic regimens. Forty nine (40%) of our patients achieved complete remission after first course of induction chemotherapy while 35% were either not in remission or had partial remission. This is in contrast to 65% CR reported in literature with standard induction chemotherapy[21]. There was superior CR rate with anthracycline based chemotherapy (39%) as compared to non anthracycline based regimens (30%) in patients with de novo AML conforming to phase 3 SWOG 9333 study showing 43% CR in patients of cytarabine/ daunorubicin arm as

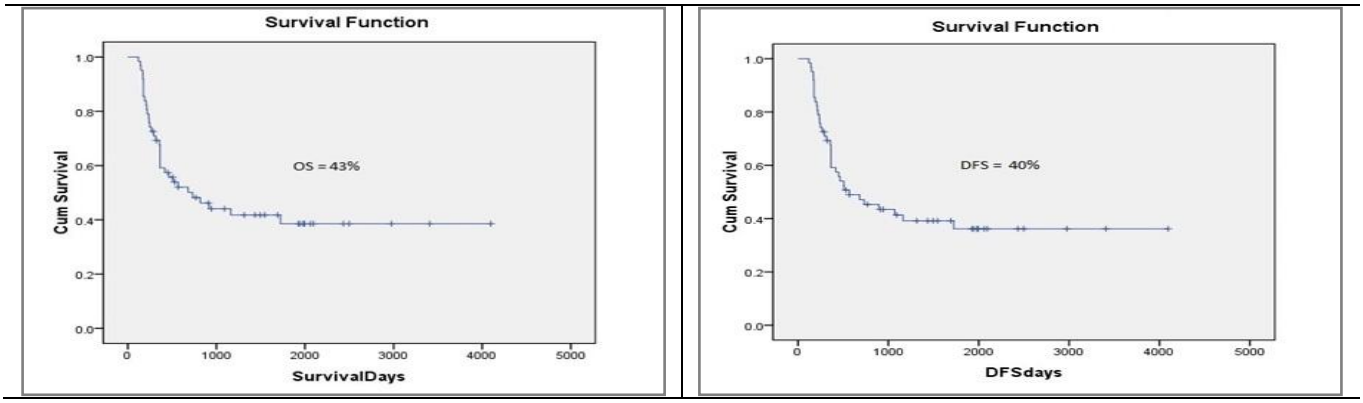

Figure: Overall survival and DFS of 62 patients who were followed up for two to five years.

compared to mitoxantrone/etoposide arm with 34% induction CR.

After exclusion of 19 induction deaths and patients who stopped treatment and were lost to follow ups, 75% of our 80 patients achieved CR after second course of chemotherapy. Our analysis has shown that out of 121 cases 60 (49.6%) patients achieved CR. Overall response after two inductions is around 50% because those patients who were in borderline remission with 5% to 7% bone marrow blasts after single course, went into morphological remission with second induction chemotherapy. Significant difference was observed between HIDAC arm and other regimens for consolidation (*p*-value 0.0168) suggesting better CR rate and overall survival in first group. One of the most important determinant of outcome in AML is cytogenetics at presentation which is required for risk stratification[24,25]. Unfortunately we only had 21 evaluable cytogenetic reports but interestingly out of four patients with t (8; 21) three are alive in CR at more than two years post treatment and one relapsed after 18 months. Four of five cases with complex cytogenetics relapsed and died within six months of treatment.

There is no standard treatment for patients with early relapse. Allogeneic bone marrow transplant (Allo-BMT) is best option for relapsed patients who have an HLA matched donor. Salvage therapy for relapsed cases is offered with aim of proceeding to Allo-BMT and or best palliative chemotherapy if BMT is not possible. In this study we have analysed 18 relapsed AML patients who were given salvage reinduction chemotherapy mostly with FLAG-Ida and I3A7 (idarubicin and cytarabine 3 ± 7) in some cases. We have observed low relapse rate in those who survived after intensive chemotherapy. All patients required aggressive blood component support and antimicrobials specially antifungals for neutropenic fever following prolonged cytopenias.

Post remission cosolidation therapy was given to 62 (51%) of our patients who achieve CR after one or two induction chemotherapy. Majority of de novo AML patients (54%) received HiDAC while other multiagent intensive regimens were given to 46% patients. Our results are compareable to Cancer and Leukemia group B study 9222 which has shown that sequential multiagent chemotherapy is not superior to HIDAC alone as post remission intensification.

Five years DFS of 8-40% is reported following consolidation chemotherapy. In our study overall survival and DFS post consolidation is 48% and 43% respectively. Overall survival and DFS of 62 patients who were followed up for two to five years is shown in figure.

CONCLUSION

A significant number of patients with AML can be saved provided proper risk adapted chemotherapy is given. Standard induction with daunorubicin/cytarabine (3 + 7) chemotherapy followed by two to three courses of high dose cytarabine is associated with overall and disease free survival in a significant proportion of cases.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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