OUTCOME OF STANDARD INDUCTION THERAPY WITH DAUNORUBICIN AND ARA-C (3+7) IN ACUTE MYELOID LEUKEMIA

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Abstract
Acute myeloid leukemia (AML) is a clonal, malignant disease of hematopoietic tissue. Main variables precluding cure are the treatment-related mortality and relapse rates. The most common induction chemotherapy regimens in AML involve the use of cytarabine (Ara-C) and an anthracycline. It was an observational study carried out in the inpatient Department of Hematology, Dhaka Medical College Hospital, Dhaka, from July 2009 to June 2014. 76 newly diagnosed cases of AML patients between 15 years to 60 year were enrolled in this study. All patient received standard induction therapy with Daunorubicin 45mg/m² I/V for 3 days and Ara-C 100mg/m² I/V over 24 hours for 7 days. A bone marrow aspirate to assess remission status was carried out at day 28+, after the peripheral recovery. The mean age of the patients were 35.12±12.45 years, ranging from 17 to 55 years. 68% were male and 32% cases were female. Total 34(44.7%) patient achieved complete remission (CR), out of them 17% had t(8;21), 5.8% had inv16 and only 2.9% was FLT3 positive. 26(34%) patient achieved partial remission (PR), 11% had t(8;21) and 3.8% inv16. 13.1% patient failed to achieve any remission (Non responder, NR) and 6 patient (7.8%) died during induction therapy. Age, performance status and cytogenetics had significant influence (P<0.025, P<0.030 and P<0.003 respectively) on the outcome. The presenting peripheral blast percent (%) also had a significant influence (P=0.012) on the outcome after induction therapy. Complete remission rate is significantly lower in our center comparing discussed study. This is probably due to lack of modern hospital facility and socio-economic condition of our patients. Cytogenetic analysis provides the most powerful independent predictor of disease outcome. To improve outcome, all the supportive measures have to be improved and more tools are required in identifying the good prognostic groups.

Introduction
Acute myeloid leukemia is a hematopoietic neoplasm that is characterized by the presence of a malignant clone of myeloid cells in the bone marrow with maturation arrest at the level of blast. It is the most common acute leukemia affecting adults. Information about risk factors and clinical results on outcomes after intensive chemotherapy can be helpful in assisting clinicians in decision making. Main variables precluding cure are the treatment-related mortality and relapse rates. Decisions on intensification, de-escalation and allografting rely on the ability to divide an apparently homogeneous group according to risk. The most common induction chemotherapy regimens in AML involve the use of cytarabine (Ara-C) and an anthracycline.

Cytarabine is usually administered as a continuous infusion of 100 to 200 mg/m²/day for 7 days, with an anthracycline given by intravenous push daily on the first 3 days of ara-C therapy, a combination called “7 + 3.” Studies performed by CALGB in the 1980s established the efficacy of this regimen for

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newly diagnosed AML and since then has been the most commonly used induction regimen for treatment of adult patients with AML. Continuous infusion of ara-C at a dosage of 100 mg/m$^2$ has been shown to be superior to pulse doses of 100 mg/m$^2$ every 12 hours. \(^2\) \(^7\ + \ 3\) \(^7\) has been shown to be superior to the same drugs given over 5 days and 2 days \((5+2)\), respectively, \(^2\) and appears equivalent to \(^10\ + \ 3\). \(^4\) Increasing the ara-C dose in \(7 + 3\) \(^7\) from 100 mg/m$^2$/day to 200 mg/m$^2$/day or prolonging the infusion to 10 days, in combination with daunorubicin, increased the toxicity with no to minimal improvement in efficacy. \(^4\) \(^5\) \(^6\) Among the chemotherapy regimens, Daunorubicin and Ara-C \((3+7)\) is the gold standard; but its response has not been evaluated in our population and ethnic diversity. Keeping this in view, this study will be undertaken to analyze the response in new AML patients admitted in Dhaka Medical College Hospital (DMCH), Dhaka. The aim of the present study was to evaluate the morphological remission status after induction therapy and find out association between patients factors with the outcome of induction therapy.

**Methods**

It was an observational study carried out in the inpatient the Department of Hematology, Dhaka Medical College Hospital, Dhaka, from July 2009 to June 2014. 76 newly diagnosed cases of AML patients between 15 year to 60 year were enrolled in this study. The diagnosis was based on morphological examination of peripheral blood film and bone marrow examination and all patient received standard induction therapy with Daunorubicin 45mg/m$^2$ I/V for 3 days and Ara-C 100mg/m$^2$ I/V over 24 hours for 7 days. Abone marrow aspirate to assess remission status was carried out at day 28+, after the peripheral recovery.

**Selection Criteria:**

**Inclusion criteria**

1. Previously untreated newly diagnosed cases of AML. The diagnosis was based on morphological examination of peripheral blood film and bone marrow examination.
2. Age of the patients between 15 years to 60 years of both sex.
3. Absence of severe cardiac diseases precluding use of anthracyclines.

**Exclusion criteria:**

1. Secondary AML
2. History of prior chemotherapy.
3. Acute promyelocyteleukaemia
4. Age less than 15 years of both sexes.
5. Age more than 60 years of both sexes.
6. Patients who have cardiac disease.
7. Patients who could not provide supportive therapy.
8. Pregnancy in 1**st** trimester.

**Data Collection:**

Relevant clinical data were recorded in the structured questionnaire after written consent. It includes background information on age, sex, positive physical examination findings, laboratory investigations.

**Results**

The mean age of the patients were 35.12±12.45 years, ranging from 17 to 55 years. Majority (32%) of the patients were in the range of 31-40 years, 88% patients fell under 50 years, only 12% patients were over 50 years. 68% were male and 32% cases were female presented with generalized weakness & tiredness (80%), fever (72%), bleeding (34%), bodyache (24%). all the patients presented with moderate to severe anaemia (100%), and most of them had bone tenderness (56%), hepatomegaly & splenomegaly (24%), lymphadenopathy (20%), purpura (16%) and gum hypertrophy (12%). Gum hypertrophy was mostly found in patients with M4/M5 variety. Majority of the patient belonged to M2 (36%) Variety, 24% patients had M4, while M0, M1, M5 and M6 subtype was 4%, 16%, 12% and 8% respectively. 56% of the patient had ECOG I, followed by ECOGII & 0 was 36% and 8% respectively. The Hb conc. was found at study entry between 3.30 to 10.80 gm/dl (mean 7.00gm/dl) and most of the patients (56%) fell within the range of 6.0-9.0 gm/dl. The total
leukocyte count (TC) was within a range between $1.3 \times 10^9$ and $230 \times 10^9$/L (mean $40.63 \times 10^9$/L) and most of the patients (60%) had a TC $<25 \times 10^9$/L. Platelet count varied from $3.4 \times 10^9$ to $665 \times 10^9$/L (mean $64.87 \times 10^9$) and 84% patients were thrombocytopenic at presentation. At presentation, blast% was within a range between 0% to 96% (mean 51.72%) and most of the patients (56%) had >50% blast.

Total 34(44.7%) patient achieved complete remission (CR), out of them 17% had t(8:21), 5.8% had inv16 and only 2.9% was FLT3 positive. 26(34%) patient achieved partial remission (PR), 11% had t(8:21) and 3.8% inv16. 13.1% patient failed to achieve any remission (Non responder, NR) and 6 patient (7.8%) died during induction therapy. Age, performance status and cytogenetics had significant influence (P<0.025, P<0.030 and P<0.003 respectively) on the outcome. The presenting peripheral blast percent (%) also had a significant influence (P=0.012) on the outcome after induction therapy. 90% cases with CR, 16.66% cases with PR and 25% cases with NR had presented with a peripheral blast percent (%) of less than 50%. On the other hand, 83.3% cases with PR, 100% cases with NR and 75% cases had a peripheral blast percent (%) over 50%.

**Fig.-1**: Distribution of the patients by FAB classification

**Fig.-2**: Relationship between age and treatment outcome

**Fig.-3**: Relationship between performance status and treatment outcome

CR: Complete remission, PR: Partial remission
NR: Non responder
In the present study, the mean age of the patients was 35.12±12.45 years, while previous study in Bangladesh by Yunus, who found 72.22 percent of AML within the age of 11-30 years and by Borua, who found 60 percent of the AML within the age of 12-40 years. Another study in Bangladesh, Hannan found 62.3 percent patients were within the range of 30-50 years. On the other hand, Bricker found median age of AML was 62-64 years, MRC median age was 50-55 years, Wiernik et al. median age was 45-50 years, Yates et al. found 70% male versus 55.42% female. The higher incidence of AML among males in our study may be due to socio-economic status, poverty, illiteracy, female patients being neglected more and get less opportunity to attend a tertiary medical centre.

In this study, clinical feature more or less similar with the findings of Borua who showed weakness in 86.66%, fever in 66.66%, gum bleeding in 26.66%, anaemia in 96.66%, hepatomegaly 43.33%, lymphadenopathy in 13.33%, bone tenderness in 40%, splenomegaly in 13.33% and purpura in 43.33%.

Younger group of patient (<50 yrs) showed better outcome (10% CR versus close to 90% CR in those younger) and P Value was 0.025; similar to study Preisler et al. and Estey et al. found poorer results in patients over age 50 years. Performance status also significant (P<0.030) which considered an important prognostic factor in AML. Remission rate is by far much inferior to the original study by Preisler et al. and Yates et al. found 75% CR, Cassileth et al. found 70% CR and Grier et al. reported 72% CR. Our Complete remission rate is significantly lower. This is probably due to lack of modern hospital facility and socio-economic condition of our patients. Being the member of least developed country, most of the patients could not bear the cost of expensive medicine and transfusion support in pancytopenic period as life supportive care.

The clinical outcome of acute myeloid leukemia (AML) is extremely variable, ranging from survival of a few days to cure. Different clinical and biological features at diagnosis are useful for the prediction of clinical outcome. The unfavorable biology of the disease, comorbidities, and significant side effects of intensive cytoreductive treatment make treatment decisions difficult, and patient information becomes essential to allow a shared decision-making process. Cytogenetic analysis provides the most powerful independent predictor of disease outcome. To improve outcome, all the supportive measures have to include:

CR: Complete remission, PR: Partial remission, NR: Non responder

Fig. 4: Relationship between cytogenetics and treatment outcome

Discussion

In the present study, the mean age of the patients was 35.12±12.45 years, while previous study in Bangladesh by Yunus, who found 72.22 percent of AML within the age of 11-30 years and by Borua, who found 60 percent of the AML within the age of 12-40 years. Another study in Bangladesh, Hannan found 62.3 percent patients were within the range of 30-50 years. On the other hand, Bricker found median age of AML was 62-64 years, MRC median age was 50-55 years, Wiernik et al. median age was 45-50 years, Yates et al. found 70% male versus 55.42% female. The higher incidence of AML among males in our study may be due to socio-economic status, poverty, illiteracy, female patients being neglected more and get less opportunity to attend a tertiary medical centre.

Regarding sex distribution, male patients (68%) were greater than female patients (32%) which is more or less similar to a previous study by Yunus who found 72.22% male versus 27.28% female and Borua who found 70% male versus 30% female. This is in contrast with the observation of Bishop et al. who found male 54% versus female 46% and Weinstein et al. who found 44.58% male versus 55.42% female. The higher incidence of AML among males in our study may be due to socio-economic status, poverty, illiteracy, female patients being neglected more and get less opportunity to attend a tertiary medical centre.

In this study, clinical feature more or less similar with the findings of Borua who showed weakness in 86.66%, fever in 66.66%, gum bleeding in 26.66%, anaemia in 96.66%, hepatomegaly 43.33%, lymphadenopathy in 13.33%, bone tenderness in 40%, splenomegaly in 13.33% and purpura in 43.33%.
be improved and more tools are required in identifying the good prognostic groups. Further large scale randomized study with a long term follow-up should be undertaken to ascertain the success of induction therapy.

References


