Anthracycline versus Non-anthracycline Induction Regimens in Patients with De Novo Acute Myeloid Leukemia

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ABSTRACT

Background & Objectives: Acute myeloid leukemia (AML) is the most prevalent form of acute leukemias in adults; unfortunately it carries very poor prognosis. Over the past decade marvelous advances were achieved in understanding pathophysiology of AML and this was reflected in management of AML patients. Nevertheless the standard anthracycline based induction regimens remained the cornerstone for treatment of AML; however their effectiveness is limited by their well known cardiotoxicity. To our knowledge this is the first study that investigated anthracycline versus non-anthracycline induction regimens in patients with AML.

Methods: 90- AML patients were enrolled in the study; they were retrospectively recruited from AML patients who were admitted at South Egypt Cancer Institute (SECI) from 2000-2010. Demographic, clinical, hematologic and data concerning treatment and therapeutic response were collected from hospital records of patients.

Results: Analysis of the collected data showed lower median age of the study participants compared to other studies, FAB M2, M3, M4, followed by M1 were the commonest FAB subtypes among the study patients. Survival analysis showed longer overall survival (OS) and progression free survival (PFS) in those treated with anthracycline induction regimens compared with the non-anthracycline treated group. Also, higher incidence of relapse was observed in the non-anthracycline group.

Conclusion: Anthracycline based induction regimens are still more effective than non-anthracycline regimens for treatment of AML, however the search for safer drugs than anthracyclines is still mandatory.

Key words: AML, anthracycline, non-anthracycline.
1. Introduction

AML is a hematopoietic stem cell disorder with devastating consequences; it has the lowest survival rate of all leukemias. (1, 2) Unfortunately, AML is the commonest acute leukemia in adults with an incidence of 2.7 per 100,000 persons, (3, 4) with increasing prevalence in the population older than 60 years of age and a median age at presentation of 65 years. (5) Worldwide, the incidence of AML is highest in the U.S., Australia, and Western Europe. (6)

Despite the remarkable advances in treatment of AML, anthracycline based induction regimens have remained the standard therapy in AMLs for more than 40-years. (7, 8) However the well known anthracycline induced cardiotoxicity limits its use in first induction in elderly patients and in those with left ventricular dysfunction. Furthermore its use in re-induction is restricted with the maximum cumulative dose over lifetime. (9)

Anthracyclines are a group of antineoplastic drugs that were first introduced in treatment of AML in 1960; daunorubicin was the first discovered and introduced anthracycline. The complete remission rates (CR) of daunorubicin based induction regimens in AML ranged from 59% - 72% in those under 60-years old; this declined to 31%-45% in those over 60-years old. (10-12) The efficacy of anthracycline was found to be dose dependent, (13- 15) nevertheless their complications are dose dependent too. (16, 17) These facts led to the emergence of non-anthracycline based induction regimens for patients with AML. The combination of fludarabine, Ara-C, and G-CSF was found to induce remission in 58% of AML patients aged ≥ 60 years, after first induction. (18) Furthermore, low-dose cytarabine was used and shown to be effective and standard in elderly AML patients. (19)

OS and PFS were used by many researchers to assess the appropriateness and efficacy of drugs used in AML. (20, 21) This study was conducted to assess the anthracycline versus the non-anthracycline based induction regimens in AML patients using OS and PFS.

2. Subject and Methods

2.1. Study population and data collection

A retrospective study was conducted at SECI, Assiut University, Assiut, Egypt. SECI is a big tertiary health care center that offers superspecialist health care to residents of nearly eight governorates of Egypt. These include, from north to south, Al Menia, Assiut, Sohage Qena, Luxor, Aswan, Al- wady Al -Jadid, and Red Sea Governorates.

Data were collected from hospital records of AML patients who were admitted at SECI in the period 2000 to 2010. Only patients with de novo AML were included in the study; however records with incomplete follow up data were excluded from the study. Both hand written and computer based hospital records were reviewed. Demographic, clinical, and hematologic data were collected; also information about treatments and treatment responses were gathered; outcome of patients was collected too. Both the anthracycline and non-anthracycline groups were matched in sex, age (±6 years) and residency.

The Eastern Cooperative Oncology Group criteria (ECOG) were used to assess how AML affected the daily life activities of the patients. Data on the ECOG Performance status of patients was recorded. The status was scaled and graded on a 5-point scale as following:

Table 1: Grades of ECOG performance status. (22)

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG Performance Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

N.B. ECOG: Eastern Cooperative Oncology Group
2.2. Diagnosis of AML in the study patients

Diagnosis of AML in our patients was dependent on clinical suspicion and laboratory certainty. The latter was accomplished with complete blood picture (C.B.C) and bone marrow examination. According to WHO recommendations blast percent of 20% or more were required for diagnosis of AML. (23) Morphological, cytogenetical and immunophenotypic examination of neoplastic cells were also performed.

2.3. Treatment of AML in the study patients

Before treatment with chemotherapy thorough clinical and laboratory investigations were performed including LFT, KFT, serum electrolytes and blood glucose, also ECG and CXR. Echocardiography was done in those at risk of cardiac dysfunction e.g. hypertension, history of cardiac disease, obesity, smoking, over 40-years old, or previous anthracycline induction. Patients received induction regimens under umbrella of good supportive care in the form of red blood cells and platelet transfusions, broad spectrum antibiotics and antifungals. Neutropenic patients were managed at the Intensive Care Unit. Those with leucocytosis > 100 underwent one setting of leukopheresis before induction. Allopurinol was administered to patients to guard against development of tumor lysis syndrome.

The choice of anthracycline or non-anthracycline based induction regimens was dependent on the possible development of cardiotoxicity. Accordingly non-anthracycline induction was prescribed as first induction in patients with left ventricular ejection fraction < 50% or for re-induction in those with maximum cumulative anthracycline dose > 100%. The latter was calculated as the total anthracycline dose received. The maximum cumulative anthracycline dose for different types of anthracycline drugs was for daunorubicin (500-600 mg/m2), doxorubicin (450-550 mg/m2), idarubicin (93 mg/m2), epirubicin (950 mg/m2), and (160 mg/m2) for mitoxantrone.(24, 25) Those who received anthracycline based regimens were treated with adriamycin (doxorubicin) 25 mg/m2 per day for 3-days and Ara C 100mg/m2 per day for 7-days by continuous Infusion. The FLAG or Low dose Ara-C regimens were prescribed for those who received non-anthracycline induction. The FLAG regimen was in the form of Fludarabine 30 mg/m2 a day IV infusion over 30 minutes, every 12 hours in 2 divided doses on days from 1-5, Ara-C 2000 mg/m2 IV infusion over 4 hours, every 12 hours in 2 divided doses, starting 4 hours after the end of fludarabine infusion on days from 1-5, and G-CSF 5 µg/kg SC from day 6 till neutrophil recovery. Those who received low dose Ara-C were treated with 20 mg/m2 cytarabine S.C. /12 hours, four days a week. Another dose was repeated after remission or whenever needed. (26- 28)

2.4. Assessment of response to treatment

Bone marrow aspirates or biopsies were performed after one week of induction. Response to treatment was defined according to the criteria developed by the International Working Group.(29) Thus CR was identified by independence from RBCs transfusion, absence of extramedullary disease and platelet & neutrophil counts >100,000/ul & >1000/ul, respectively. Bone marrow aspiration or biopsy reveals <5% blast with absence of Auer rods and normal maturation of all cellular elements of blood were also needed to define CR. On the other hand Partial response was defined as normal CBC and >50% decline of bone marrow blasts. If patient developed complications either of the disease or the treatment he/she was categorized in the group of complicated disease. Disease free survival was considered as the time from when the patient is rendered free of clinically detectable cancer until recurrent cancer is diagnosed.

Progression free survival was estimated as the time from the start of treatment to the first documentation of objective tumor progression or death as a result of any cause. Date of mortality was assessed to calculate the overall survival, which is the time from start of study treatment to date of death as a result of any cause.

2.5. Statistical analyses

The collected data were verified, coded by the researcher and analyzed by using the Statistical Package for Social Sciences (SPSS/PC/VER 17). Follow up data of AML patients attending SECI from 2000 to 2010 were also analyzed. Descriptive statistics, mean, standard deviation, and frequencies, were calculated. Test of significances Chi square test was used to compare the difference in distribution of frequencies of remission and relapse in the two induction groups. Kaplan-Mayer and Survival analysis was calculated. Significant test results were considered when p value was < 0.05.

2.6. Ethical considerations

The study design, objectives and methods were consistent with both the declaration of Helsinki and the guidelines of the research ethical committee at SECI. Furthermore, agreement of the Vice Dean of SECI was obtained before handling patients’ records.

Results

3.1. Characteristics of the study participants

A total of 90 AML patients were enrolled in the study; their mean age was 37.9 ± 6.9 and 51.1% were males, with a male to female ratio 1:0.41. The vast majority of the studied group was from Assiut governorate (44%) while the least frequency was from both Red Sea and Al- wadi Al- Jadid governorates (1%) and Figure 1 shows the distribution of the study group over governorates of Upper Egypt. Their ECOG performance status ranged from 1-2. Marked leukocytosis was observed in 4 (4.4%) of patients where their total Leukocytic count was >100,000. Only 5(5.6%) patients had CNS infiltration. As we are interested in determining the efficacy of anthracyclines we classified regimens used to two groups; the first group includes regimens which contain anthracyclines (n=74), while the second group is without anthracyclines (n= 16). Response to treatment was non remission in 28 patients (31.1%) and 62 patients achieved remission after induction chemotherapy (68.9%), as depicted in Table 2.
Table 2: Characteristics of the study participants (n=90).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD)</td>
<td></td>
<td>37.9 ± 6.9</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>46 (51.1%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>44 (48.9%)</td>
</tr>
<tr>
<td>Performance State</td>
<td>1</td>
<td>76 (84.4%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>14 (15.6%)</td>
</tr>
<tr>
<td>Total Leukocytic Count</td>
<td>&lt; 100.000</td>
<td>86 (95.6%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 100.000</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>CNS infiltration</td>
<td>No</td>
<td>85 (94.4%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5 (5.6%)</td>
</tr>
<tr>
<td>Regimens used for induction</td>
<td>Anthracycline</td>
<td>74 (82.2%)</td>
</tr>
<tr>
<td></td>
<td>Non-anthracyline</td>
<td>16 (17.8%)</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Remission</td>
<td>62 (68.9%)</td>
</tr>
<tr>
<td></td>
<td>No Remission</td>
<td>28 (31.1%)</td>
</tr>
</tbody>
</table>

Figure 1: Distribution of AML patients over 8 governorates of Egypt
Patients had different FAB subtypes; however M2 and M3, M4 followed by M1 were the most frequent subtypes among the study group, 21.1% and 17.8%, respectively. In the hospital records of 7.8% of AML patients’ data about AML type was missing. Figure 2 shows AML FAB subtypes in the study group.

3.2. Survival Analysis of Anthracycline vs non-anthracycline treated patients

3.2.1. Overall survival:

When we compared survival and response between treatment groups, we found that the anthracycline group showed better survival than the other group which was statistically highly significant (p value =0.0022), as in Table 3 and Figure 3.

Table 3: Overall survival of Anthracycline treated group vs non-anthracycline

<table>
<thead>
<tr>
<th>Survival time(months)</th>
<th>No. Exposed to Risk</th>
<th>Survival proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anthracycline</td>
<td>Non anthracycline</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
3.2.2. Progression free survival:

There was a statistically significant difference between anthracycline and non anthracycline groups (p value =0.0021). Median progression free survival of anthracycline group is 10 months. In non anthracycline group, 13 patients out of 16 suffered from relapse, while the remaining 3 patients showed remission after induction, but didn’t continue follow up at our institute as in Table 4 and Figure 4.

Table 4: Progression free survival of Anthracycline treated group vs non-anthracycline.

<table>
<thead>
<tr>
<th>Survival time(months)</th>
<th>No. Exposed to Risk</th>
<th>Survival proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anthracycline</td>
<td>Non anthracycline</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
AML is a hematological malignancy that is characterized by marked clinical and genetic heterogeneity. Over the past 20 years extensive research was conducted in a trial to develop new targeted therapies for AML and improve its prognosis. Nevertheless, treatment of non-APL AML is still dependent on the standard 3/7 induction regimen of the anthracycline antibiotic and the cell cycle specific agent cytarabine. CR is obtained in 25%-75% of newly diagnosed patients with this regimen. Cardiotoxicity of anthracycline was found to be dose dependent and limits its use in re-induction. (30-33) This research was conducted to assess the outcome of patients with AML treated with induction regimens containing anthracycline drugs versus those treated with non-anthracycline regimens. The main objective was to prove or disprove the efficacy of non-anthracycline drugs in AML in a trial to recommend the inclusion of these agents in first induction.

Acute myeloid leukemia (AML) presents in all ages but is mainly a disease of the elderly with a median age of 69 years in the white US population, but in our study median age was 37 years. The life expectancy of Egyptians is 72 years compared to 78 years for the Americans and almost 95% of the Egyptians are below 60 years compared to 13% for the Americans. (34-36) So usually at SECI the number of young patients is more than the old patients; this may be due to exposure to hazardous chemicals (benzene) or to radiation and it is reported that many of the adult cases with leukemia are cigarette smokers, (37, 38) and usually young adults seek medical advice more than elder ones.

In our country, Adriamycin is the most commonly used anthracyclin in induction of remission other than daunorubicin or idarubicin, as it is the more available and cheaper. The last study that reported the use of Adriamycin in treatment of AML was in 1982, comparing the use of Adriamycin (30 mg/m2) versus daunorubicin (30 mg/m2 and 45 mg/m2). Response rate for Adriamycin was 58% compared to 59% and 72% for daunorubicin. (31) Interestingly, the use of Adriamycin in 3 and 7 regimens in this study achieved remission rate as high as 69%; almost similar to high dose daunorubicin when used for induction of remission in the above mentioned study.

In Yates et al study, (31) they included all AML patients without considering the cytogenetic type or patients’ performance, which were later proved to have a strong impact on the response to induction. This probably resulted in including some patients who are expected not to respond well or more prone to toxicity. This is a major confounding factor which may affect the usefulness and the validity of the result. (43) Unfortunately, no other studies tried to re-investigate the use of Adriamycin in a prospective randomized controlled trial to prove or disprove the usefulness of its use in AML. The results reported in this study added more evidence encouraging the use of Adriamycin as a cheaper anthracyclin alternative to the more expensive types in 3 and 7 regimens.

The main concern about the use of Adriamycin in the management of AML is higher incidence of toxicity. Based on our experience the dose of Adriamycin routinely used is 25 mg/m2. This dose is effective as we reported much less toxic side effects than the ordinary dose (30 mg/m2). Recently risk
of Adriamycin toxicity has markedly reduced as many natural antioxidants are proved to prevent Adriamycin toxicity including vitamin E, vitamin C, coenzyme Q, carotenoids, vitamin A, flavonoids, polyphenol, resveratrol, antioxidant from virgin olive oil and selenium. (32)

Low-dose cytarabine is recommended for elderly patients (above 75 years). (43) However in our practice we may use this regimen for younger patients (50 to 75 years old) due to poor performance status and associated co-morbidities which are relatively common among Egyptian patients. Results of the current study showed longer OS and PFS in the anthracycline treated AML patients compared to the non-anthracycline group after fixation of other risk factors e.g. age, ECOG performance status. Furthermore a higher rate of relapse was observed in the non-anthracycline treated group.

In conclusion this study showed that despite the well known toxicity of the anthracycline chemotherapeutics, they still have a superior efficacy compared to the non-anthracyline drugs. Accordingly non-anthracyline drugs could not be recommended for first induction in younger age AML patients. However the search for drugs safer than anthracyclines is mandatory.

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References


