Cytosine arabinoside, mitoxantrone, and etoposide in the treatment of adult patients with previously untreated acute myeloid leukemia

Mohammed S. Harakati, MB, FRCPC, FACP.

ABSTRACT

Objectives: The study was conducted to examine the efficacy and tolerability of a three-drug regimen in newly diagnosed, previously untreated adult patients with acute myeloblastic leukemia.

Methods: Forty-eight consecutive adult patients with newly diagnosed, previously untreated de novo acute myeloid leukemia were entered into this prospective single arm study. All patients received induction chemotherapy consisting of five consecutive days of each of the following three drugs: (i) cytosine arabinoside (100 mg/m²/d), (ii) Mitoxantrone (10 mg/m²/d), and (iii) etoposide (100 mg/m²/d). Patients entering into complete remission following one or two induction cycles went to receive one more cycle of identical therapy as consolidation therapy.

Results: The complete remission rate was 79%. Seventy-six percent of patients achieving complete remission required one cycle while 24% required two cycles of induction therapy. There were six deaths during induction and five deaths during consolidation. The median duration of the complete remission was 11 months and the median survival for patients achieving complete remission was 15 months. Three patients had an event-free survival of 28-36 months. The regimen was well-tolerated with mild non-hematological toxicity.

Conclusion: The combined use of cytosine arabinoside, mitoxantrone, and etoposide in the doses specified is both effective and tolerable as a therapeutic option for adult patients with newly diagnosed, previously untreated de novo acute myeloid leukemia.

Keywords: Acute myeloid leukemia, treatment, chemotherapy.


Modern therapy for acute myeloid leukemia (AML) began with the introduction of cytosine arabinoside and daunorubicin almost three decades ago. With either of these agents, 30 to 40% of adults attained a complete response and a small proportion of these patients was long-term survivors. Further significant improvement occurred with the introduction of combination chemotherapy for AML induction. Initial combination consisted of cytosine arabinoside, daunorubicin and 6-thioguanine forming together the so-called “TAD” regimen. Most investigators have now eliminated 6-thioguanine from the standard AML induction regimen since its inclusion was not shown to improve overall results.

Although there is no single standard induction regimen, the most widely used combination chemotherapy for the treatment of newly diagnosed patients with AML has been the so-called “3+7”...
regimen consisting of three days of an anthracycline, usually daunorubicin in a daily dose of 45 mg/m² and seven days of cytosine arabinoside in a daily dose of 100-200 mg/m² delivered by continuous intravenous infusion.\(^9\) With this regimen 50 to 75% of patients are expected to achieve complete remission.\(^9,11\) The duration of the complete remission obtained by this regimen has been in the range of 10-18 months.\(^7,9,12\)

Attempts to improve the complete remission rate and duration have led investigators to utilize intensified dose regimen and to explore newer chemotherapeutic agents known to have antileukemic efficacy. The present study describes the efficacy and tolerability of a three-drug regimen consisting of cytosine arabinoside, mitoxantrone and etoposide as an induction regimen in newly diagnosed previously untreated adult patients with de novo acute myeloid leukemia.

**Methods.** This is a prospective, single arm study in which patients 13-60 years of age with unequivocal diagnosis of de novo AML who had not received prior antileukemic therapy were enrolled. Patients with blood or bone marrow dysplastic disorders were excluded from the study, as were patients who had received prior therapy for any other malignant disease. All patients were treated at King Khalid University Hospital in Riyadh during the period January 1994 through June 1996. The diagnosis of AML was established on the basis of peripheral blood examination, examination of the bone marrow aspirate and trephine biopsy and flowcytometric immunophenotyping according to the standard technique. Cytogenetic analyses were performed in the majority of patients. The classification of AML was carried out according to the revised French American British (FAB) subtyping.

**Treatment plan.** The induction regimen consisted of five consecutive days of each of the following drugs: (i) Cytosine arabinoside 100mg/m²/day delivered by continuous intravenous infusion, (ii) Mitoxantrone 10mg/m²/day given intravenously over 15 minutes, and (iii) Etoposide 100mg/m²/day delivered by one-hour intravenous infusion. Patients with residual disease with more than 5% blast cells in the bone marrow at day 28 of treatment for the time of adequate count recovery if this happened sooner than day 28 were given a second course of the same induction regimen. Patients failing to achieve complete remission following a second induction treatment were considered to have refractory disease and would have been evaluated for alternative therapy. Patients achieving a complete remission after one or two induction cycles were given an additional cycle of the same drug regimen as a consolidation treatment within four weeks after achieving complete remission. No further therapy was given afterward for patients maintaining their remission except for four patients who had undergone allogeneic HLA-matched related bone marrow transplantation.

**Supportive care.** Transfusion of blood components was based on pre-written conditional orders according to the results of the daily blood work. Two units of leukocyte-depleted packed red cell concentrates were transfused for hemoglobin values less than 90g/L. Leukocyte-depleted six random donor units of platelets or one single donor platelets collection were transfused for platelet counts less than 20x10⁹/L on the daily blood counts. Additional platelet transfusions were given prior to any invasive procedure and for bleeding episodes according to the individual needs.

Empirical broad spectrum antibiotic coverage was initiated following a full septic work-up in all patients who showed a single episode of oral temperature >38.5°C or two consecutive episodes of temperature in the range 38.0-38.2°C over four hours period unrelated to blood component therapy. The initial antibiotic regimen consisted of a combination of cefazidime and amikacin in appropriate dosing given every 12 hours. Vancomycin could be added, unless included in the initial coverage in the occasional patient, to the initial antibiotic regimen if fever persisted for 48 hours while the microbiological cultures were still not conclusive. Empirical antifungal treatment with amphotericin B would be added if fever persisted for an additional 48 hours after the inclusion of vancomycin and the fever remained microbiologically unexplained. Antifungal coverage would be further optimized according to the results of the microbiological cultures.

All patients underwent Hickman’s indwelling central venous catheter insertion prior to, or soon after the initiation of their treatment. One gram of intravenous vancomycin was given prophylactically to all patients one hour prior to catheter insertion.

**Evaluation of response.** Determining the remission status and defining the response to therapy required, in addition, to clinical assessment and routine blood work, bone marrow examination at least once on day 28 of treatment or sooner if count recovery took place earlier. Bone marrow examination was repeated weekly if hematological recovery did not occur by day 28 and until a conclusive response status could be defined. Complete remission (CR) was defined as <5% blast cells in a bone marrow examination, normalization of the peripheral blood counts, and the complete resolution of all clinical evidence of the disease. Partial remission (PR) required similar criteria but associated with more than 5% blast cells in the bone marrow. Deaths after inclusion in the study was categorized as "too early," if it occurred within the first two weeks of induction or consolidation...
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Figure 1 - Survival of 23 patients who achieved CR requiring frequent blood component support. The median time for ANC to exceed 0.5x10^9/L was 21.5 days (range: 15-30 days). The median time for platelets count to exceed 50x10^9/L was 24 days (range: 17-31 days). Non-hematological toxicities were mild and consisted of grade II mucositis occurring in 12 occasions (14%); and grade II gastrointestinal toxicity in the form of controllable nausea and vomiting and/or mild diarrhea occurring in 66 occasions (78%). Grade II-III alopecia was observed virtually in all patients. No treatment-related renal, hepatic, cardiac, or neurological toxicities were encountered.

Remission duration and survival. Of the 33 patients who survived through their consolidation treatment, follow-up data was available on 28 patients as four patients underwent allogeneic bone marrow transplantation elsewhere and a fifth patient was lost to follow up. The median CR duration for these 28 patients was 11 months (range: 2-36 months). Data on survival is available on 23 patients. The median overall survival was 15 months (range 4-36 months). Three patients are still alive in first CR; two at 36, and one at 28 months following entering CR. All other evaluable patients have died. Figure 1 illustrates the survival pattern in these 23 CR patients.

Discussion. Our previous experience in the treatment of adult AML patients with the so-called "3+7" regimen consisting of three days of daunorubicin and seven days of cytosine arabinoside indicated a compatible remission rate but inferior remission duration and survival to that published in the literature. Some of this suboptimal response to therapy could be accounted for, at least partially, by the predominance of AML with monocytic components; namely, FAB-M4 and M5 subtypes in our patients’ population. The predominance of these subtypes of leukemia in Saudi Arabia has also been noted by others. Both of these types of leukemia are believed to behave differently from the remaining AML subtypes. Lowered response rate has been described with the M4-AML. In addition, patients with monocytic leukemias are reported to have decreased CR rates, early relapses, failure to achieve a second remission and decreased survival.

In an attempt to improve the treatment outcome in our adult patients with previously untreated AML, two agents with antileukemic activity were added to cytarabine: namely, etoposide (VP-16-213) and mitoxantrone. Etoposide is a semisynthetic epipodophyllotoxin, which has a different mechanism of action than the anthracyclines, antihistamines or cytosine arabinoside, has been shown to be synergistic to cytarabine in vitro. The inclusion of etoposide in the standard “3+7” in an Australian Leukemia Study Group trial demonstrated

Results. Patients. Forty eight consecutive adult patients fulfilling the inclusion criteria of the study were entered over a 30 month period extending from January 1994 to June 1996. There were 27 males and...

21 females with a median age of 35.5 years (range 13-54 years). There were 22 Saudis, 16 non-Saudi Arabs, and 10 patients of different Asian nationalities. The frequency of various FAB subtypes was 1, 2, 4, 7, 18, 15, 0, and 1 patient with M0, M1, M2, M3, M4, M5, M6, M7.

Treatment outcome: (i) Remission induction: Of the 48 patients entered into the study 38 patients (79%) achieved CR. Twenty nine patients of these 38 patients (76%) required one cycle of induction therapy while 9 patients (24%) required two cycles of therapy to achieve CR. There were 4 patients (8%) with refractory disease. Early deaths occurred in 2 patients (4%) while death during neutropenia occurred in 4 patients (8%). Five of these 6 deaths were attributed to sepsis while the remaining one death occurred secondary to pulmonary hemorrhage.

(ii) Consolidation therapy: All the 38 patients entering CR were given an identical course of therapy as a consolidation treatment. Thirty three patients completed their treatment successfully. There were two early and three neutropenic deaths during the consolidation period. All deaths were attributed to sepsis. Progressive pulmonary infiltrate leading to respiratory failure occurred in three of these deaths.

Hematological recovery data and toxicity. All patients suffered, as expected, grade IV hematological toxicity with severe pancytopenia...
significant improvement in remission duration and survival in previously untreated patients with AML who were less than 55 years of age. We found the results of this study quite encouraging to include etoposide in the induction regimen. In addition, acute monocytic leukemia, a predominant type of leukemia in our patients, was found to be the most sensitive type of leukemia to etoposide when used as a single agent. Several other reports have described a potential activity of etoposide against acute leukemia with monocytic features when used alone or in combination with other drugs. Mitoxantrone, on the other hand, was included in our induction regimen on the basis of the observation that it had a significant anti-leukemic activity in phase I and II trials.

At least, a comparable degree of efficacy and toxicity to that of daunorubicin has been demonstrated in a randomized multicentral trial in previously untreated adult patients with AML. This study did also show two trends: a lesser number of patients required two cycles of induction to achieve remission, and a higher response rate in patients less than sixty years of age in the mitoxantrone arm than in the daunorubicin arm. Thus the inclusion of mitoxantrone in our induction regimen was felt to be, at least, as effective as daunorubicin with the potential of improving results of therapy.

Little data is available on the combined use of this three drug regimen in de novo previously untreated patients with AML. The same regimen in different dosing has, however, been used with encouraging results in a limited number of patients with relapsed or refractory AML. There have been, however, no phase III trials to examine this combination. Most therapeutic AML trials, unless randomized, compare their outcome with the conventional “3+7” regimen.

With such regimen, a CR rate of 53 to 72% and a median remission duration of 10 to 18 months have been reported. The CR rate of 79% obtained in our study patients compares favorably with the CR rate of the “3+7” regimen as reported in the literature and in our own hands in a similar group of 52 AML patients we previously treated. The median duration of the first CR in the study group was 11 months. This remission duration is essentially similar to that reported in the literature and is definitely superior to the CR duration we obtained with the “3+7” regimen where the median duration of the first CR was only 32 weeks. Fewer number of patients in the study group required more than one induction cycle when compared with our previous group of patients treated with the “3+7” regimen (24% versus 35%). Three of the study patients for whom adequate follow up was available are alive and in sustained CR for 28-36 months. These patients are probably cured; a result that we had not encountered with the “3+7” regimen. It should, however, be emphasized here that caution needs to be exercised when comparing the results of patients’ outcome in various series with different study design. This is particularly true when historical controls are used for such comparison.

The regimen utilized in the study was well-tolerated and had minimal non-hematological toxicities. The duration of the myelosuppressive effect of the regimen was acceptable with a median recovery time of ANC to more than 0.5x10^9/L and platelets count to more than 50x10^9/L of 21 and 24 days respectively. The rate and pattern of infectious complications encountered during the study period were essentially unchanged from those we encountered during the use of more conventional therapy in patients with acute leukemia and during the febrile neutropenic episodes in patients treated for non-hematological malignancies.

In conclusion, the combined use of cytosine arabinoside, mitoxantrone, and etoposide as an induction regimen for previously untreated adult patients with AML is both tolerable and at least as effective as the conventional “3+7” as reported in the literature although it seems to be superior to “3+7” in our patients in whom AML with monocytic features predominate. The role of etoposide in AML induction regimen for patients in whom the predominant features are M-4 and M-5 needs to be better defined by future clinical trials.

References
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