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

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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 (100mg/m²/d), (ii) Mitoxantrone (10mg/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”
Treatment of AML... Harakati

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. With this regimen 50 to 75% of patients are expected to achieve complete
remission. The duration of the complete remission obtained by this regimen has been in the
range of 10-18 months.

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 anti-
leukemic 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 histories of prior myeloproliferative or

myelodysplastic 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 (or at 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 prophylactically transfused
for platelets counts less than 20x10^9/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 >38.3°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 ceftazidime and amikacin in appropriate dosing
given eight and twelve hourly. Vancomycin would
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 amphoterecin B
would be added if fever persisted for an additional 48
hours after the inclusion of vancomycin and the fever
remained micro-biologically unexplained.
Antimicrobial 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 normocellular bone marrow, 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 (i) early death, if it occurred within
the first two weeks of induction or consolidation.
Figure 1 - Survival of 23 patients who achieved CR

Treatment, or (ii) death during neutropenia, if it occurred after the first two weeks of therapy but before recovering an absolute neutrophilic count (ANC) of 0.5 x 10^9/L or more. When consolidation therapy is completed, patients were monitored at monthly basis for the first year and every two months during the second and subsequent years. Bone marrow examinations were not routinely done during the monitoring period unless clinically indicated.

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 MO, 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 requiring frequent blood component support. The median time for ANC to exceed 0.5 x 10^9/L was 21.5 days (range: 15-30 days). The median time for platelets to exceed 50 x 10^9/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, anthraquinones 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
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 based on 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 multicenter 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