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Intensive consolidation chemotherapy for newly diagnosed acute myeloid leukemia using a regime containing moderate dose cytosine arabinoside and mitoxantrone

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Fifty patients with previously untreated acute myeloid leukemia were treated with an induction regimen consisting of cytosine arabinoside 100 mg/m^2 per day by 18 h i.v. infusion for 7 days, daunorubicin 50 mg/m^2 per day by i.v. bolus injection for 3 days and etoposide 75 mg/m^2 per day by 1 h i.v. infusion for 7 days. Thirty seven of them (74%) went into complete remission (CR) and they all then received two consecutive courses of consolidation chemotherapy consisting of cytosine arabinoside 500 mg/m^2 per day by 1 h i.v. infusion every 12 h for 4 days (total eight doses) and mitoxantrone 12 mg/m^2 daily by 30 min i.v. infusion for 3 days. They were followed by maintenance chemotherapy with cytosine arabinoside and thioguanine 2 monthly. With a median follow up time of 24 months, 20 of the 37 complete responders had relapsed (54%). The disease-free survival (DFS) of 37 CR patients and the overall survival of all patients at 24 months were 37 and 44%, respectively. Age of patients and number of courses of induction chemotherapy to achieve CR were significant factors predicting DFS. Myelosuppression was the major toxic side effect. Ten patients had prolonged marrow suppression following consolidation chemotherapy. In conclusion, despite the significant myelosuppression observed, overall improvement in treatment outcome was not demonstrable with the use of this intensive consolidation therapy.

Key words: Acute myeloid leukemia, mitoxantrone.

Introduction

Induction chemotherapy for acute myeloid leukemia (AML) usually consists of cytosine arabinoside and daunoruicin with or without other agents such as thioguanine or etoposide.[1,2] It is followed by at least two more courses of consolidation chemotherapy, often using similar drugs but at attenuated doses. Although remission is achieved in a majority of the cases, most patients eventually relapse and cure is possible in only a minority of all patients treated.[1,2] Attempts are made to improve the leukemia-free survival (LFS) of these patients by intensifying therapy, including the use of bone marrow transplantation.[3,4]

Mitoxantrone has been used together with other agents, commonly cytosine arabinoside, in treating both previously treated or untreated patients with AML.[5–28] A regime consisting of moderate dose cytosine arabinoside and mitoxantrone has been used and shown to have good activity in patients with refractory/relapsed disease.[28] We present here our initial experience in using a similar regimen as consolidation therapy for patients with previously untreated AML achieving complete remission (CR) after conventional dose cytosine arabinoside, daunorubicin and etoposide.[28,29]

Materials and methods

Fifty patients below the age of 60 years with previously untreated AML, who were seen at Queen Mary Hospital (n = 35), Queen Elizabeth Hospital (n = 13) and Princess Margaret Hospital (n = 2), entered this study between July 1991 and December 1992. Pretreatment assessment included history and physical examination, complete blood counts, blood biochemistry, peripheral blood and bone marrow examination, coagulation tests (prothrombin time, activated partial thromboplastin time and fibrinogen level), and chest radiograph.

All patients had more than 30% blast in their bone marrow. Acute leukemias transforming from myelodyplastic syndrome or chronic myeloid leukemia were excluded. Patients were classified according to the FAB system.[30] Cytochemical staining for Sudan Black, PAS, chloroacetate esterase, non-specific

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esterase and acid phosphatase was carried out. Myeloperoxidase staining was used when the result of Sudan Black staining was equivocal. Patients were diagnosed as having AML if they showed compatible morphology and positive staining for Sudan Black or myeloperoxidase. Immunophenotyping and chromosome analysis were performed only on selected cases.

Patients were hydrated and given 300 mg allopurinol daily before the start of chemotherapy. Induction chemotherapy consisted of cytosine arabinoside 100 mg/m^2 per day by 18 h i.v. infusion for 7 days, daunorubicin 50 mg/m^2 per day by i.v. bolus injection for 3 days and etoposide 75 mg/m^2 per day by 1 h i.v. infusion for 7 days.[29] If CR was not achieved, a second course of identical treatment was given. If the patient entered CR, two consecutive courses of consolidation chemotherapy consisting of cytosine arabinoside 500 mg/m^2 per day by 1 h i.v. infusion every 12 h for 4 days (total eight doses) and mitoxantrone 12 mg/m^2 daily by 30 min i.v. infusion for 3 days were given immediately after the marrow recovered.[28] Patients remaining in CR after the consolidation chemotherapy were given a 2-monthly maintenance chemotherapy for 2 years, which consisted of cytosine arabinoside 100 mg/m^2 subcutaneously daily for 5 days and thioguanine 100 mg/m^2 orally daily for 5 days.

Standard criteria for responses and failures were employed.[31] The Kaplan–Meier product limit method was used to generate DFS and overall survival curves. DFS time was measured from the date of first remission to the date of first relapse and the overall survival time was measured from the date of diagnosis to the date of death or last follow-up. The log-rank procedure was used to compare survival curves, and the χ^2 test with Yates' correction was used to compare CR and relapse rates.

Results

A total of 50 patients entered the study. The clinical characteristics of these 46 patients are shown in Table 1. Thirty seven (74%) of them received one course of induction chemotherapy and the other 13 (26%) had two. A total of 37 (74%) of them went into CR. The causes of induction failure in the remaining 13 (26%) patients were refractory disease in two, partial remission in three and hypoplastic death in eight (four due to bleeding and four to infection). The median follow-up time of the 37 complete responders was 24 months and 20 of them (54%) had relapsed at that time. Six of the 20 relapses occurred at the time of consolidation therapy and 14 during maintenance. The DFS of the 37 complete responders and the overall survival curves of all 50 patients are shown in Figures 1 and 2. The DFS or CR patients and the overall survival of all patients at 24 months were 37 and 44%, respectively.

Nine relapsed patients received a marrow transplant at early first relapse or second CR (eight from HLA-identical siblings and one from a matched unrelated donor). Three of them are still alive in CR, including the one receiving marrow from a matched unrelated donor, at 11, 12 and 33 months post-transplant.

None of the clinical and laboratory characteristics, including sex, age, FAB morphology, hepatos-

Table I. Clinical characteristics

	No. of patients
Total no. of patients	50 (100%)
Sex	
male	30 (60%)
female	20 (40%)
Age (years)	
median	33.5
range	14–60
Morphology (FAB)	
M0	1 (2%)
M1	9 (18%)
M2	15 (30%)
M3	9 (18%)
M4	11 (22%)
M5	3 (6%)
M6	2 (4%)
Hepatosplenomegaly	7 (14%)
Initial white cell count (10^9/l)	
mean	42.7
range	0.2–305
Infection at diagnosis	22 (44%)

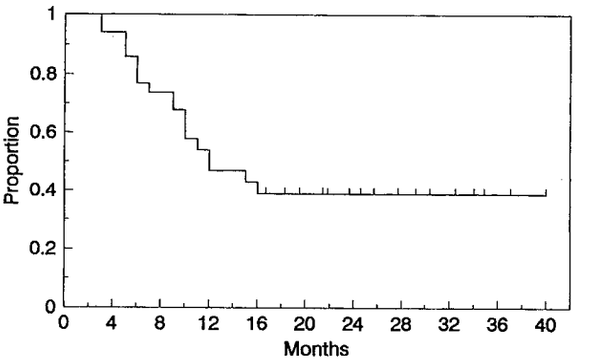

Figure 1. The DFS of the 37 complete responders.

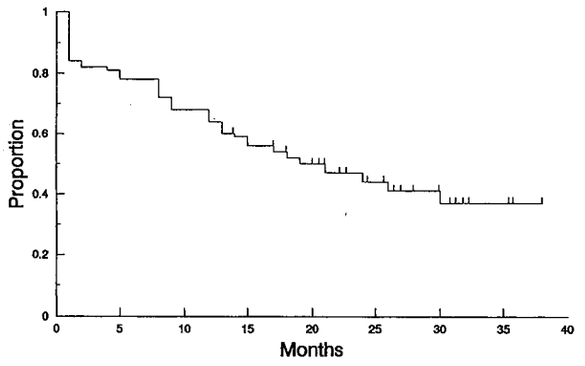

Figure 2. The overall survival of all 50 AML patients.

plenomegaly, initial white cell count and infection at presentation, predicted clinical response to the induction regimen. However, age and number of courses of induction chemotherapy to achieve CR were significant factors predicting DFS. CR patients below 40 years of age had a better DFS at 24 months of 56% compared with that of 14% in patients above 40 years ($p = 0.03$). The DFS of CR patients requiring two courses of induction therapy was 0% at 24 months compared with 48% for those requiring only one ($p = 0.006$). Younger patients (below 40 years) had significantly better overall survival (60% versus 39%, $p = 0.01$).

Myelosuppression was the major toxic side effect following induction chemotherapy. For patients achieving CR, the median time to granulocyte ($> 0.5 \times 10^9$) and platelet ($> 20 \times 10^9$) recovery was 17 (range 13–31) days and 12 (range 10–21) days, respectively. Forty-one of them had neutropenic fever including 12 confirmed or presumed episodes of fungal infections and 17 pneumonia. Non-hematological toxicities were acceptable. All patients experienced nausea and vomiting, which were usually controllable.

Significant myelosuppression was also observed during the intensive consolidation phase. Following the first consolidation, the median time to granulocyte ($> 0.5 \times 10^9$) and platelet ($> 20 \times 10^9$) recovery was 15 and 11 days, respectively. Following the second consolidation, the median time to granulocyte ($> 0.5 \times 10^9$) and platelet ($> 20 \times 10^9$) recovery was 19 and 13 days, respectively. Twenty-seven of them had neutropenic fever during the first or second consolidation, including 10 confirmed or presumed episodes of fungal infections. Ten patients had prolonged marrow suppression confirmed by marrow examination with a neutrophil count of $< 1.0 \times 10^9$ or platelet count of $< 100 \times 10^9$ for more than 60 days.

Discussion

The standard induction chemotherapy consisting of cytosine arabinoside and daunorubicin with or without thioguanine is successful in 60–70% of the patients.[1–3] However, the median remission duration of the complete responders is often less than 12 months, and prolonged remission and possibly cure is achievable in only around 20–30% of all patients.[1–3]

Attempts are made to improve the treatment results by modifying the induction regimen, such as increasing the dose of cytosine arabinoside, replacement of daunorubicin by idarubicin, addition of etoposide or using hematopoietic growth factor to 'sensitize' the leukemic cells.[32–40] The consolidation phase has also been modified by increasing the dose of cytosine arabinoside or introducing non-cross-resistent agents other than those used in the induction phase.[41] The use of autologous or allogeneic bone marrow transplantation may also improve the prognosis. However, allogeneic transplantation is only possible in a minority of patients who have HLA-compatible donors and the question of marrow purging for autologous transplantation remains unresolved.[42–45]

Mitoxantrone is an effective agent for the treatment of AML.[6–29] When this drug was given alone to patients with refractory or relapsed disease, CR lasting for 2–6 months was observed in 20–40% of the patients. Mitoxantrone has also been given in combination with other drugs such as cytosine arabinoside or etoposide. Clinical trials have used a relatively high dose of cytosine arabinoside together with mitoxantrone giving CR rates of 20–50% in refractory or relapsed AML patients. When mitoxantrone is used in the induction regimen to treat newly diagnosed AML patients, the results appeared to be comparable to the standard daunorubicin containing regimen.

A regimen consisting of moderate dose cytosine arabinoside and mitoxantrone has been shown to be effective in inducing a second CR in patients with refractory or relapsed AML.[29] A similar regime was used in the consolidation phase of this trial in the hope of improving the treatment results.

We have previously employed an identical induction chemotherapy regimen for our AML patients but with identical drugs at an attenuated dose being given for consolidation. A total of 46 patients were treated and a CR rate of 67% was achieved. The DFS of CR patients and overall survival of all patients were 45 and 40%, respectively.[29] The treatment outcome of patients receiving the moderate dose cy-

tosine arabinoside and mitoxantrone consolidation did not appear to be superior to this historic control.

Significant myelosuppression was observed in our patients following the moderate dose cytosine arabinoside and mitoxantrone consolidation. Prolonged pancytopenia was seen in some patients and three of the 37 CR patients (8.1%) died at the consolidation phase as a result of toxicity. Another study has also revealed more prolonged cytopenia in AML patients receiving mitoxantrone at the induction phase.[36]

Conclusion

Despite the significant myelosuppression observed, overall improvement in treatment outcome was not demonstrable with the use of this intensive consolidation therapy. However, significantly better DFS and overall survival were seen in patients below the age of 40. Also, patients requiring two courses of induction chemotherapy had a significantly poorer DFS.

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