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Short communication

Induction chemotherapy for newly diagnosed acute myeloid leukaemia using a regime containing cytosine arabinoside, daunorubicin and etoposide

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Summary. A total of 46 patients with previously untreated acute myeloid leukaemia were treated with an induction regimen consisting of 100 mg/m^2 cytosine arabinoside given daily by 18-h i.v. infusion for 7 days, 50 mg/m^2 daunorubicin given daily by i.v. bolus injection for 3 days and 75 mg/m^2 etoposide given daily by 1-h i.v. infusion for 7 days. In all, 30 patients (67%) went into complete remission and were given further consolidation and maintenance chemotherapy. Of the 31 complete responders, 15 (48%) relapsed. The median disease-free survival of the 31 complete responders and the median overall survival of all 46 patients were 25 and 14 months, respectively. None of the clinical characteristics, which included sex, age, FAB morphology, extramedullary diease and initial WBC count, predicted the clinical response. Myelosuppression was the major toxicity and non-haematological side effects were acceptable. The regimen appeared to have acceptable toxicity, and its efficacy was comparable with that of standard regimens.

Induction chemotherapy for acute myeloid leukaemia (AML) usually consists of cytosine arabinoside and daunorubicin, with or without thioguanine [3, 5]. Although this regimen induces remission in a majority of cases, most patients eventually relapse and cure is possible in only a minority of patients treated [3, 5]. Etoposide has been shown to have activity against AML [2, 4, 10]. Preclinical studies [8] have also indicated synergism between cytosine arabinoside and etoposide. However, no large series has reported the incorporation of etoposide into the standard induction regimen for patients with previously untreated AML. We present our initial experience with a regimen consisting of conventional doses of cytosine arabinoside, daunorubicin and etoposide in patients with previously untreated AML.

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Patients and methods

A total of 46 patients (age, >60 years) with previously untreated AML, who were seen in the Department of Medicine, University of Hong Kong, Queen Mary Hospital, entered this study between January 1984 and October 1989. Pretreatment assessment included a 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 a chest radiograph.

The blast-cell content of the bone marrow was >30% in all patients. Acute leukaemias transforming from myelodysplastic syndrome or chronic myeloid leukaemia were excluded. Patients were classified according to the FAB system [1]. Cytochemical staining for Sudan black, PAS, chloroacetate esterase, non-specific 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.

Patients were hydrated and given 300 mg allopurinol daily before the start of chemotherapy. Induction chemotherapy consisted of 100 mg/m^2 cytosine arabinoside given daily by 18-h i.v. infusion for 7 days, 50 mg/m^2 daunorubicin given daily by i.v. bolus injection for 3 days and 75 mg/m^2 etoposide given daily by 1-h i.v. infusion for 7 days. If complete remission (CR) was not achieved, a second course of identical treatment was given. If the patient entered CR, two consecutive courses of consolidation chemotherapy using similar doses of cytosine arabinoside for 5 days, daunorubicin for 2 days and etoposide for 5 days were given immediately after the marrow had recovered. Patients remaining in CR after consolidation chemotherapy were treated for 2 years with maintenance chemotherapy, given in 2-months cycles, which consisted of (a) cytosine arabinoside and thioguanine; (b) cytosine arabinoside, vincristine and prednisone; (c) cytosine arabinoside and daunorubicin; and (d) cytosine arabinoside, vincristine, and prednisone. The dosing schedule included: cytosine arabinoside, 100 mg/m^2 given daily ×5; thioguanine, 100 mg/m^2 p.o. given daily ×5; vincristine, 2 mg i.v. given as a single bolus injection; prednisone, 40 mg/m^2 given daily ×5; and daunorubicin, 50 mg/m^2 i.v. given as a single bolus injection. Daunorubicin was replaced by thioguanine when the cumulative dose exceeded 550 mg/m^2.

Standard criteria for responses and failures were employed [11]. The Kaplan-Meier product-limit method was used to generate disease-free survival (DFS) and overall survival curves. DFS was measured from the date of first remission to the date of first relapse, and overall survival 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 chi-square test with Yates' correction was used to compare CR and relapse rates.

Table 1. Clinical characteristics

	Number of patients (%)
Total number of patients	46 (100%)
Sex: Men	27 (59%)
Women	19 (41%)
Age (years): Median	36
range	15–58
Morphology (FAB): M1	14 (30%)
M2	7 (15%)
M3	8 (17%)
M4	7 (15%)
M5	10 (22%)
Extramedullary disease: Lymph node	2 (4%)
Liver	6 (13%)
Spleen	8 (17%)
Skin	2 (4%)
Gum	2 (4%)
Initial WBC count ($\times 10^9$/l): <4.0	6 (13%)
4.0–10	9 (20%)
10–50	18 (39%)
50–100	3 (7%)
>100	10 (22%)

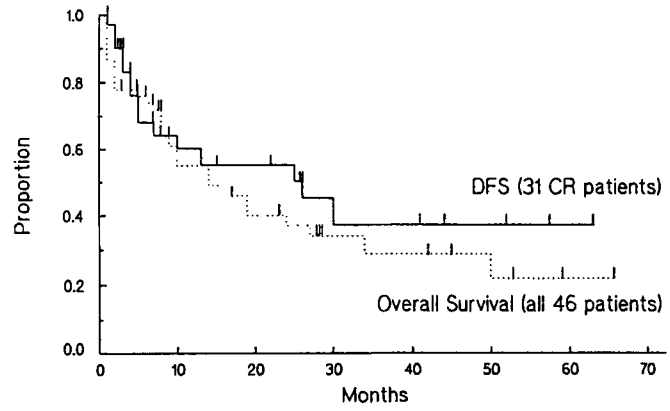

Fig. 1. Disease-free survival (*DFS*) of the 31 complete responders (*CR*) and overall survival of all 46 AML patients

Results

A total of 46 patients entered the study, 10 of whom were involved in a randomised study comparing the present regimen with one lacking etoposide. Their clinical characteristics are shown in Table 1. In all, 31 (67%) patients went into CR (in 28 cases, after one course of induction chemotherapy; in 3, after two courses). The causes of induction failure in the remaining 15 patients were refractory disease in 3 cases, partial remission in 5 and hypoplastic death in 7 (4 cases of bleeding and 3 of infection). Of the 31 complete responders, 15 (48%) relapsed. The median follow-up for complete responders was 17 months. Of the 15 relapses, 5 occured at the time of consolidation therapy; 9, during maintenance chemotherapy; and 1, thereafter.

The DFS of the 31 complete responders and the overall survival curves for all 46 patients are shown in Fig. 1. The median DFS of CR patients and the median overall survival of all 46 patients were 25 and 14 months, respectively. None of the clinical characteristics, which incuded sex, age, FAB morphology, extramedullary disease and initial WBC count, predicted the clinical response to the regimen.

Myelosuppression was the major toxicity of this regimen, with nadir counts occurring within the first 2 weeks. For patients achieving CR, the median time to granulocyte ($>0.5\times 10^9$) and platelet ($>50\times 10^9$) recovery was 17 (range, 13–31) days and 12 (range, 10–21) days, respectively. In all, 20 patients had serious infections and 8 had severe bleeding problems. Non-haematological toxicities were acceptable. All patients experienced nausea and vomiting, which were usually controllable. Severe mucositis occurred in five patients.

Discussion

In the last two decades, there has been an improvement in the outcome of patients with AML [3, 5]. However, standard induction chemotherapy consisting of cytosine arabinoside and daunorubicin, with or without thioguanine, is not successful in 30%–40% of patients [3, 5]. The median duration of remission in complete responders is often <12 months, and prolonged remission is possible in only around 20% of all cases [3, 5]. Although the use of autologous or allogeneic bone marrow transplantation might improve prognosis, allogeneic transplant is possible in only a minority of patients who have HLA-compatible donors, and successful remission induction is required for all patients [9]. Therefore, more effective induction therapy for AML is necessary.

Etoposide has been shown to be effective in treating AML, and it may be more effective in diseases with a monocytic component such as M4 or M5 [2, 5, 6, 7, 10]. The efficacy and the toxicity of an induction/consolidation regimen containing cytosine arabinoside, daunorubicin and etoposide were evaluated in the present study. This regimen appeared to have acceptable toxicity, and its efficacy was comparable to with that of standard regimen. Probably due to the small number of patients in each subgroup, none of the patient characteristics, which included the M4 and M5 morphology, predicted the clinical response. Prospective randomised studies comparing this regimen with one lacking etoposide are currently being conducted to determine more confidently the value of etoposide in the treatment of AML and to investigate its possible benefit to the subset of patients with M4 and M5 morphology.

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Note added in proof: Early result of the randomised trial suggests that the addition of etoposide results in significantly improved remission duration but not survival (Blood 75: 27–32, 1990).