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Short communication

Salvage chemotherapy containing moderate-dose cytosine arabinoside and mitoxantrone for relapsed and resistant acute myeloid leukaemia

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Summary. A total of 29 evaluable patients with acute myeloid leukaemia (AML) either in relapse or resistant to initial induction daunorubicin-containing chemotherapy were given a salvage regimen consisting of moderate-dose cytosine arabinoside and mitoxantrone. There were 8 (28%) complete responders (CRs), 4 (14%) partial responders (PRs), and 17 (52%) nonresponders. The duration of CRs was 2+, 2+, 3+, 3, 4+, 4, 5 and 6 months respectively. Two of the eight CR patients were refractory to initial daunorubicin-containing induction therapy and another two had achieved a previous CR lasting <6 months. Four of the eight CR patients had received an amsacrine-containing salvage regimen (ATA) prior to administration of the present moderate-dose cytosine arabinoside and mitoxantrone regimen; this indicates the lack of absolute clinical cross-resistance between the present combination and the daunorubicin- or amsacrine-containing regimens. However, the duration of CRs achieved by these patients remains very short and should, if possible, be followed by allogeneic or autologous bone marrow transplantation.

Introduction

Although a majority of patients who have been newly diagnosed as having acute myeloid leukaemia (AML) can be induced into clinically complete remission, most patients eventually relapse. Various salvage chemotherapy regimens can induce a second remission in 25%–50% of patients with refractory or recurrent disease, but the remission is often of brief duration. Mitoxantrone has been shown to be active against leukaemia and has been used in combination with various doses of cytosine arabinoside for the treatment of AML [2–5, 8–10]. We report the results we obtained using a salvage regimen consisting of mitoxantrone and a moderate dose of cytosine arabinoside in patients with refractory or relapsed AML.

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Patients and methods

Patients with AML either in relapse or resistant to initial daunorubicin-containing induction chemotherapy were eligible for the present study. Cases were morphologically classified according to the FAB classification [1]. Patients with chronic myeloid leukaemia or myelodysplastic syndrome were excluded. A WHO performance status of 0 or 1 was required for entry into the study. Patients were given a regimen consisting of 500 mg/m^2 cytosine arabinoside infused i.v. over 1 h every 12 h for eight doses and 12 mg/m^2 mitoxantrone infused i.v. over 0.5 h daily for three doses. Those who achieved a complete remission were given two more identical courses of treatment as consolidation therapy.

Standard criteria for responses and failures were used [11]. Treatment failures were classified as follows: type I, significant drug resistance (failure to produce significant marrow aplasia); type IIa, relative drug resistance (after marrow aplasia, repopulation of marrow by leukaemic cells within 40 days following the completion of therapy); type IIb, partial remission (marrow, 5%–10% blast cells; peripheral blood, <5% blast cells); type III, regeneration failure (marrow remains hypoplastic for >40 days after the completion of therapy); type IV, hypoplastic death (expiration of patients during the period of marrow hypoplasia occurring at <40 days after the completion of therapy); type V, inadequate trial (expiration of patients at <7 days after the completion of therapy with the patient having a cellular marrow); type VI, haematological remission in the presence of extramedullary disease.

Results

A total of 29 patients entered this study; their characteristics are shown in Table 1. Each subject received 1–4 courses of therapy. Of these 29 patients, 15 received the moderate-dose cytosine arabinoside and mitoxantrone regimen immediately after failing the initial daunorubicin-containing induction regimen (conventional-dose cytosine arabinoside, daunorubicin with or without etoposide) and 14 had additionally received an amsacrine-containing salvage regimen (conventional-dose cytosine arabinoside, thioguanine and amsacrine; ATA) [6, 7]. There were 8

Table 1. Patients' characteristics

Total number of patients	29
Sex:	
M	14
Female	15
Median age (range)	37 (13–63) years
Morphology:	
M1	8
M2	9
M3	1
M4	5
M5	6
Initial induction therapy:	
Cytosine arabinoside/daunorubicin	10
Cytosine arabinoside/daunorubicin/etoposide	19

Data represent the number of patients unless otherwise indicated

Table 2. Response to moderate-dose cytosine arabinoside and mitoxantrone according to the response to previous therapy

		Response to MDAC/MTX		
		CR	PR	NR
Response to initial daunorubicin-containing induction therapy:				
Refractory	10	2	1	7
CR, <6 months	6	2	1	3
CR, >6 months	13	4	2	7
Response to ATA salvage regimen:				
Refractory	10	2	1	7
CR, <6 months	4	2	1	1
CR, >6 months	0	0	0	0

Data represent the number of patients responding; MDAC/MTX, moderate-dose cytosine arabinoside and mitoxantrone

(28%) complete responders (CRs), 4 (14%) partial responders (PRs), and 17 (52%) nonresponders. The duration of the CRs was 2+, 2+, 3+, 3, 4+, 4, 5 and 6 months, respectively. Two of the eight CR patients were refractory to initial daunorubicin-containing induction therapy and another two had achieved a previous CR lasting <6 months. Four of the eight CR patients had received a salvage ATA regimen prior to the administration of the present moderate-dose cytosine arabinoside and mitoxantrone regimen (Table 2).

Of the 21 treatment failures, 3 were type I; 10, type IIa; 4, type IIb; 1, type III; and 3, type IV. No type V or VI failure was observed. The cause of death in the four type II failures was septicaemia in three cases and cerebral bleeding in one. Myelosuppression was the major toxic side effect of this regimen. There were 34 febrile episodes, of which infective organisms or foci of infection were found in 10. All patients experienced nausea and vomiting. Severe mucositis occurred in four patients. There was no treatment-related hepato-, cardio- or neurotoxicity.

Discussion

Mitoxantrone is an effective agent for the treatment of AML. When this drug was given alone to patients with refractory or relapsed disease, a CR rate of 20%–40% (CR duration, 2–6 months) was observed. Mitoxantrone has also been given in combination with other drugs such as cytosine arabinoside and etoposide. Many trials have used a relatively high dose of cytosine arabinoside together with mitoxantrone; the CR rates vary from 20% to 50%, but the duration of the CRs achieved remains short [2–5, 8–10].

As the neurotoxicity of cytosine arabinoside is dose-dependent, we chose to use only a moderate dose of cytosine arabinoside in the present study. Myelosuppression was the major toxicity in this trial and non-haematological side effects were acceptable. Neuro- and cardiotoxicities were not seen. The efficacy of this regimen appeared to be comparable with that of the other salvage regimens used. In our previous study using conventional-dose cytosine arabinoside, thioguanine and amsacrine (ATA) to treat relapsed and resistant AML, CRs proved to be very uncommon in patients who either were resistant to daunomycin or had achieved a CR lasting <6 months following initial daunorubicin-containing induction therapy [6]. However, using this moderate-dose cytosine arabinoside and mitoxantrone regimen, a CR could be achieved in 4 of the 26 (25%) patients who either were refractory to or had achieved CR lasting <6 months following the initial daunorubicin-containing induction therapy [7]. Moreover, 4 of the 14 (29%) patients who had failed previous treatment with the ATA regimen achieved a CR after treatment with the present moderate-dose cytosine arabinoside and mitoxantrone regimen. This indicates that there is no absolute clinical cross-resistance between this combination and daunorubicin- or amsacrine-containing regimens [6]. However, the duration of CRs achieved by these patients remains very short and should, if possible, be followed by allogeneic or autologous bone marrow transplantation.

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