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Chemotherapy for relapsed and resistant acute nonlymphoblastic leukemia

Effect of ATA, an amsacrine-containing regime

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Summary. Twenty-nine evaluable patients with acute nonlymphoblastic leukemia (ANLL), either in relapse or resistant to initial induction therapy (ara C, daunorubicin + etoposide), received the ATA regime consisting of 100 mg/m^2 per day Ara C by i.v. infusion for 4–5 days, 100 mg/m^2 per day thioguanine orally for 4–5 days, and 100 mg/m^2 per day amsacrine i.v. for 2–5 days. Each patient received 1–6 courses (median, 2) of the regime. There were 7 (24%) complete responders, and their duration of responses were 2, 2, 2, 5, 9$^+$, 19, and 24$^+$ months. The complete remission (CR) rate of patients who had a previous CR beyond 6 months (6/13, 46%) was significantly better ($X^2 = 4.25$, $p < 0.05$) than that of those who had previously relapsed within 6 months or were refractory to primary induction chemotherapy (1/16, 6%). The two groups of patients had similar patterns of treatment failure. Myelosuppression was the major toxic side effect, and nonhematological toxicities were mild and acceptable.

Introduction

Although intensive chemotherapy for patients with newly diagnosed, acute nonlymphoblastic leukemia (ANLL) induces complete remission in a majority of the cases, most patients eventually relapse [6]. Using various chemotherapeutic salvage regimens, remission can be achieved in 25%–50% of patients with refractory or recurrent leukemia. However, with rare exceptions, second remissions are often of brief duration [6].

Amsacrine is an active agent for the treatment of ANLL [6, 7]. When it is used in combination with ara C and thioguanine, a complete response rate of 32% has been reported [2]. We present our results of a regime consisting of ara C, thioguanine, and amsacrine (ATA) in patients with refractory or relapsed ANLL.

Methods

Patients with ANLL, either in first relapse or resistant after >3 courses to initial daunorubicin-containing induction chemotherapy, were eligible for the study. Cases were classified morphologically according to the FAB system [4]. Patients with chronic myeloblastic leukemia or myelodysplastic syndrome were excluded. Their performance status was 0 or 1 (WHO) before entering the study. They were given the ATA regime consisting of 100 mg/m^2 per day ara C by 18-h i.v.infusion for 4–5 days, 100 mg/m^2 per day thioguanine orally for 4–5 days, and 100 mg/m^2 per day amsacrine by 1-h i.v. infusion for 2–5 days. Patients were given ara C, thioguanine, and amsacrine for 4, 4, and 2 days, respectively, for their first course, and the doses were gradually escalated to 5, 5, and 5 days, respectively, for subsequent courses. Those who achieved complete remissions were maintained on 100 mg/m^2 per day ara C subcutaneously for 5 days and 100 mg/m^2 per day thioguanine orally for 5 days every 8 weeks. Standard criteria for responses and failures were employed [12]. Treatment failures were classified into:

A. Type I – significant drug resistance (failure to produce significant marrow aplasia)

B. Type IIa – relative drug resistance (after marrow aplasia, leukemic cells repopulate marrow within 40 days of completion of therapy)

C. Type IIb – partial remission (marrow, 5.1%–20%, and peripheral blood, <5% blast cells)

D. Type III – regeneration failure (marrow remains hypoplastic for >40 days after completion of therapy)

E. Type IV – hypoplastic death (patient expires during period of marrow hypoplasia occurring <40 days after completion of therapy)

F. Type V – inadequate trial (patient expires <7 days after completion of therapy with a cellular marrow)

G. Type VI – (hematologic remission, but extramedullary diseases persist)

The complete response rates and their differences are expressed with confidence intervals (CI) [8].

Results

Table 1 shows the patients characteristics. Each patient was given 1–6 courses (median, 2) of ATA, and a total of 61 courses were carried out. The number of days of treatment with ara C, thioguanine, and amsacrine were, respectively, 4, 4, and 2 in 41 courses; 4, 4, and 3 in 8; 4, 4, and 4 in 3; and 5, 5, and 5 in 9. There were 7 (24%) complete responders (CR), 3 (10%) partial responders (PR), and 19 (66%) nonresponders. The duration of responses were 2, 2, 2, 5, 9$^+$, 19, and 24$^+$ months for CR and 2, 2, and 4 months for PR. There were 1 CR (24$^+$ months) and 1 PR (2 months) among patients with refractory ANLL. The CR rate of patients who had a previous CR beyond 6 months

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Table 1. Patients' characteristics (no. of patients)

1. Total no. of patients		29
2. Sex: male		15
female		14
3. Age (years):	median	40
	range	16–72
4. Morphology:	M1	16
	M2	4
	M3	1
	M4	2
	M5	6
5. Previous therapy:		
	Ara C/daunorubicin	22
	Ara C/daunorubicin/VP-16	7
6. Responses to previous therapy:		
	Refractory	8
	CR <6 months	8
	CR >6 months	13

(6/13, 46%, 90% CI, 26%–68%) was significantly better ($X^2 = 4.25$, $p < 0.05$) than that of those who had previously relapsed within 6 months or were refractory to primary induction chemotherapy (1/16, 6%, 90% CI, 1%–23%). The 95% CI for the differences in CR rates was 40%±29%.

Of the 7 treatment failures who had a previous CR beyond 6 months, 2 had type IIa, 2 had type IIb, 1 had type III (died of septicemia), and 2 had type IV (septicemia, 1, and cerebral hemorrhage, 1). Of the 15 treatment failures who had previously relapsed within 6 months or were refractory to primary induction therapy, 3 had type I, 8 had type IIa, 1 had type IIb, and 3 had type IV (septicemia, 2, and cerebral hemorrhage, 1). There were no type V or VI failures. For the 6 type III or IV failures, the causes of death were septicemia in 4 and cerebral hemorrhage in 2.

Myelosuppression was the major toxic side effect of this regime. The nadir counts occurred within the first 1–2 weeks. In patients achieving CR, the median time to granulocyte ($>0.5 \times 10^9$/l)and platelet ($>50 \times 10^9$/l) recovery were 19 (range, 13–29) and 15 (range, 8–19) days, respectively.

There were 51 febrile episodes, of which infective organisms or foci of infection could be found in 20 (11, septicemia; 4, pneumonia; 2, anal sepsis; and 3, oral sepsis). Nonhematologic toxicities were mild. All patients experienced nausea and vomiting, and had mild phlebitis at injection sites. Mild to moderate stomatitis occurred in 69% of the patients; the severity appeared to correlate with the number of days of therapy undergone. There was no hepato-, cardio- or neurotoxicity related to the treatment.

Discussion

Amsacrine is an effective agent in patients with resistant ANLL [6, 7]. When the drug is used alone at a dose of 100–150 mg/m^2 per day for 5 days, remissions were achieved in 20%–30% of patients with disease resistant to ara C and anthracyclines. Amsacrine is also used in various combinations with other drugs such as 5-azacytidine, ara C, etoposide, and thioguanine [1, 5, 6, 9, 11]; however, there is no evidence that these combination regimes are superior to amsacrine alone [1, 6].

Our ATA regime appeared to be more effective in relapsed ANLL patients who had a previous CR induced by daunorubicin-containing regimes and lasting more than 6 months. The CR rate of patients who had a previous CR beyond 6 months was significantly better than that of those who relapsed within 6 months or were refractory to primary induction therapy (46% vs 6%). However, most responses were only of short duration. The two groups of patients had similar patterns of treatment failure.

Myelosuppression was the major toxic side effect of the ATA regime. The aplastic deaths were probably contributed to by uncontrolled leukemia as well as drug toxicity. On the other hand, the nonhematologic toxicities of the regime were mild and acceptable. This may be due to the conservative doses of drugs used. Although all patients had received daunorubicin as part of their initial induction therapy, amsacrine-related cardiotoxicity was not observed [10].

More effective use of amsacrine in the management of ANLL needs to be further exlpored. The combination of amsacrine and high-dose ara C appears to produce a remission rate superior to that achieved with amsacrine alone, but the combination may not be superior to that achieved with high-dose ara C alone [3, 6, 13]. Clinical trials are also under way in various centers to evaluate regimes incorporating amsacrine into consolidation programs following complete remissions [6].

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References

1. Arlin ZA (1983) Current status of amsacrine (AMSA) combination chemotherapy program in acute leukemia. Cancer Treat Rep 67: 967–970
2. Arlin ZA, Gee TS, Kempin SJ, Mertelsmann R, Dellaquila C, Andreeff M, Clarkson BD (1981) Treatment of adult nonlymphoblastic leukemia (ANLL) with amsacrine in combination with cytosine arabinoside (ara C) and 6thioguanine (AAT). Proc Am Assoc Cancer Res 22: 172
3. Arlin ZA, Gaddipati J, Ahmed T, Mittelman A, Friedland M, Rieker E (1985) Treatment of acute leukaemia with amsacrine and high dose cytarabine. Cancer Treat Rep 69: 1001–1002
4. Bennet JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Garlnick HR, Sultan C (1985) Proposed revised criteria for the classification of acute myeloid leukaemia – a report of the French-American-British cooperative group. Ann Intern Med 103: 626–629
5. Dhaliwal HS, Shannon MS, Barnett MJ, Prentice HG, Bragman K, Malpas JS, Lister TA (1986) Treatment of acute leukaemia with m-AMSA in combination with cytosine arabinoside. Cancer Chemother Pharmacol 18: 59–62
6. Gale RP, Foon K (1987) Therapy of acute myelogenous leukaemia. Semin Hematol 24: 40–54
7. Legha SS, Keating MJ, McCredie KB, Bodey GP, Freireich EJ (1982) Evaluation of AMSA in previously treated patients with acute leukaemia: results of therapy in 109 adults. Blood 60: 484–490
8. Simon R (1986) Confidence intervals for reporting results of clinical trials. Ann Intern Med 105: 429–435
9. Tschopp L, Von Fliedner VE, Sauter C, Maurice P, Gratwohl A, Fopp M, Cavalli F (1986) Efficacy and clinical cross-resistance of a new combination therapy (AMSA/VP-16) in previously treated patients with acute non-lymphocytic leukaemia. J Clin Oncol 4 (3): 318–324

10. Weiss RB, Grillo-Lopez AJ, Marsoni S, Posada JG Jr, Hess F, Ross BJ (1986) Amsacrine-associated cardiotoxicity – analysis of 82 cases. J Clin Oncol 4: 918–928
11. Worsley AM, Catovsky D, Goldman JM, Galton DAG (1984) New combination chemotherapy for relapsed acute myeloid leukaemia. Lancet i: 1232
12. Zittoun R, Preisler HD (1984) Reporting treatment results in non-solid tumours. In: Buyse ME, Staquet MJ, Sylvester RJ (eds) Cancer clinical trials, methods and practice. Oxford: Oxford University Press, p 139–156
13. Zittoun R, Bury J, Stryckmans P, Lowenberg B, Peetermans M, Rozendaal KY, Haanen C, Kerkhofs M, Jehn U, Willemze R (1985) Amsacrine with high dose cytarabine in acute leukaemia. Cancer Treat Rep 69: 1447–1448

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