Cancer Chemother Pharmacol (1989) 23: 401–402

Cancer Chemotherapy and Pharmacology

Short communication

Fractionated anthracycline therapy in acute myeloblastic leukaemia in adults

Sarah M. Donohue and Brian J. Boughton

Department of Haematology, Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2TH, UK

Summary. A total of nine adults with newly diagnosed acute myeloblastic leukaemia (AML) and seven with relapsed disease were treated with fractionated daunorubicin in combination with cytosine arabinoside and 6-thioguanine. Remissions were seen in 89% and 57%, respectively. The side effects associated with bolus injections of daunorubicin were much less severe with fractionated treatment, and there was no significant cardiotoxicity despite total doses of up to 1363 mg/m^2 daunorubicin. These results show that fractionated anthracyclines are effective in the treatment of AML and that this mode of administration may permit an upward revision of the accepted dose limits for anthracyclines.

Introduction

Successful remission induction of acute myeloblastic leukaemia (AML) is seen in approximately 70% of adult patients treated with combinations of daunorubicin, cytosine arabinoside and thioguanine (DAT) [9]. However, conventional anthracycline therapy is limited by a dose-releated cardiotoxicity [7], which is associated with a high mortality and is difficult to predict in individuals using non-invasive cardiological techniques [3]. For this reason, somewhat arbitrary limitations have been placed on the total dose of anthracyclines permitted in individual cases, and this restricts their therapeutic usefulness [1]. The present study is an attempt to use anthracyclines in such a way as to circumvent this.

Anthracyclines are less cardiotoxic when given by continuous infusion or in fractionated doses [4, 6], but prelimary studies have shown that they are still effective in AML when used this way [2, 8]. The present report is an update of our own experience with fractionated anthracycline therapy in adult AML.

Patients and methods

Fifteen consecutive, unselected adults with de novo or relapsed AML were diagnosed according to the French-American-British (FAB) classification and treated with fractionated DAT (F-DAT) for 5–10 days. Daunorubicin was given as an infusion in 100 ml *N* saline solution over 30 min at a dose of 10–15 mg/m^2. Cytosine-arabinoside was given as a bolus i.v. injection at 100 mg/m^2 twice daily, and thioguanine was given orally at a dose of 100 mg/m^2 twice daily. Complete remissions were defined as a bone marrow count with $<5\%$ blasts and normal peripheral blood counts. Patients with less than $<5\%$ marrow blasts but reduced peripheral blood counts were classified as having partial remissions. Patients were nursed in isolation facilities and supported as necessary with antibiotics and transfusion therapy. They were monitored for clinical evidence of cardiotoxicity and underwent regular electrocardiographic and echocardiographic examinations.

Table 1 shows a group of nine patients, aged 17–76 years, with newly diagnosed AML and various FAB sub-types. Seven of nine patients (78%) showed complete remissions after receiving between 228 and 533 mg/m^2 daunorubicin. Treatment was extremely well tolerated, with little diarrhoea and vomiting and no instances of alopecia. Eight of these patients showed no evidence of congestive cardiac failure or cardiac dysrhythmias; however, one (patient 6) presented with heart failure and arterial flutter before any chemotherapy was given but went on to receive 238 mg/m^2 daunorubicin without further cardiac complications.

Table 2 shows a group of seven patients, 17–77 years of age, with relapsed disease. Five patients were aged >60 years and two were over 70 years of age. Responses were

Table 1. Patients with de novo AML

Patient number	Age	FAB type	Cumulative dose of DNR (mg/m^2)	Outcome
1	20	M1	533	PR
2	74	M1	320	CR
3	68	M6	199	CR
4	36	M6	406	CR
5	31	M2	445	CR
6[a]	54	M4	238	CR
7	59	Not given	228	CR
8	76	M1	353	CR
9	17	M2	347	No response

Nine patients presenting de novo with AML, showing their age at presentation and the FAB leukaemia sub-type. The cumulative dose of daunorubicin (DNR) is given, and the response to therapy is shown as a complete remission (CR), partial remission (PR) or no response as defined in the text

[a] Patient 6 presented with cardiac failure and atrial flutter before any chemotherapy was given

Offprint requests to: B. J. Boughton

Table 2. Patients with relapsed AML

Patient number	Age	FAB type	Cumulative dose of DNR (mg/m²)	Outcome
10	17	Not given	1150	CR
11	30	M2	1363	CR
12	61	M2	500	No response
13[a]	62	M4	403	No response
14	68	M1	688	PR
15	76	M1	420	PR
16	76	M1	635	No response

See Table 1 for abbreviations

[a] Patient 13 had developed cardiac problems during previous non-fractionated anthracycline therapy

Table 3. Left ventricular cavity dimensions (cm)

Patient number	Systolic	Diastolic
10	3.0	5.0
	4.0	4.5
11	2.2	3.2
	2.8	4.0
12	–	–
	–	–
15	2.1	4.5
	1.7	4.2

The systolic and diastolic ventricular cavity dimensions (in cm) before and after fractionated anthracycline treatment in patients with relapsed disease. The patient numbers refer to the patients listed in Table 2. In patient 12, the cardiology report showed no significant changes in ventricular dimensions

seen in four of seven cases (57%): two complete and two partial responses. One patient (no. 13) had developed cardiac failure 12 months previously during a course of non-fractionated anthracycline therapy. These patients received between 420 and 1363 mg/m² daunorubicin, but none showed any clinical evidence of cardiomyopathy. No significant ECG changes were seen in six, but one 68-year-old patient with a history of angina and myocardial infarction showed an asymptomatic reduction of >30% in the height of the QRS complexes after receiving 688 mg/m² daunorubicin. In two patients the echocardiographic windows were too narrow to permit useful recordings of myocardial function, but Table 3 shows that in four others there was no echocardiographic evidence of deteriorating myocardial dysfunction.

Discussion

This study shows that fractionated anthracycline therapy is extremely effective when used for remission induction in adult AML. In newly diagnosed leukaemia, the 78% complete remission induction rates are comparable or superior to the remission rates reported in large studies using conventional anthracycline administration. The treatment was well tolerated, and the diarrhoea, vomiting and alopecia encountered with conventional therapy was not seen in these cases. In this respect, fractionated anthracyclines are particularly useful in ill, debilitated or elderly patients or for out-patient treatment.

In relapsed patients, the 57% remission rate we observed is, again, comparable with those previously reported in larger studies [5]. These patients received between 403 and 1363 mg/m² of anthracycline, but none of them showed evidence of significant cardiotoxicity. In some series in which anthracyclines are given by conventional bolus injection, cardiotoxicity has been reported in up to 40% of patients given more than 600 mg/m², and in these the mortality may be as high as 50% [3, 7].

We have now extended these observations in relapsed patients who have already received the recommended total doses of anthracyclines and in patients who are elderly or have pre-existing heart disease. The total dose of conventional anthracyclines is limited by cardiotoxicity, and consolidation therapy with these agents has shown only a marginal improvement in patient survival [7, 9]. Since the present study suggests that fractionated anthracycline therapy can be extended far beyond the present recommended dose limits, trials should now be carried out to evaluate the effectiveness of extended consolidation treatment with anthracyclines.

Acknowledgements. We acknowledge the support of the Leukaemia Research Fund and Farmitalia Limited and would like to thank Judith Crompton for secretarial assistance.

References

1. Blum RH, Carter SK (1974) Adriamycin. A new anticancer drug with significant clinical activity. Ann Intern Med 80: 249
2. Boughton BJ, Franklin IM, Apperley J, Knight D (1984) Non-cardiotoxic anthracycline regimens in the treatment of acute myeloblastic leukaemia. Br J Haematol 58: 378
3. Bristow MR, Mason JW, Billingham ME, Daniels JR (1978) Doxorubicin cardiomyopathy: evaluation by phonocardiography, endomyocardial biopsy and cardiac catheterisation. Ann Intern Med 88: 168
4. Chlebowski T, Paroly WS, Pugh RP, Hueser J, Jacobs EM, Pajak TF, Bateman JR (1980) Adriamycin given as a weekly schedule without a loading course: clinically effective with reduced incidence of cardiotoxicity. Cancer Treat Rep 64 (1): 47
5. Gale RP, Foon KA (1986) Acute myeloid leukaemia. Recent advances in therapy (Clinics in haematology, vol 15, no. 3, chap 10). W. B. Saunders, London
6. Legha SS, Benjamin RS, Mackay B, Ewer M, Wallace S, Valdivieso M, Rasmussen SL, Blumenschein GR, Freidreich E (1982) Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. Ann Intern Med 96: 133
7. Lenaz L, Page JA (1976) Cardiotoxicity of adriamycin and related anthracyclines. Cancer Treat Rev 3: 111
8. Lewis JP, Meyers FJ, Tanaka L (1985) Daunomycin administered by continuous intravenous infusion is effective in the treatment of acute nonlymphocytic leukaemia. Br J Haematol 61: 261
9. Rees JKH, Gray RG, Swirsky D, Hayhoe FGJ (1986) Principal results of the Medical Research Council's 8th Acute Myeloid Leukaemia Trial. Lancet ii: 1236

Received March 18, 1988/Accepted September 5, 1988