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Short-term Therapy for Acute Myelogenous Leukaemia in Younger Patients

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A. Introduction

It has now been repeatedly demonstrated that it is possible to achieve complete remission (CR) in the majority of younger adults with acute myelogenous leukaemia (AML) [4, 5, 7, 11, 12], and that approximately one-fifth of patients in whom this is achieved will continue well without recurrence for many years [2, 6, 8, 10]. These observations have naturally stimulated considerable research in to how these achievements may be translated into cure being probable for the majority rather than possible for the minority. In general, the trend has been to increase the quantity of initial therapy to the limits of bone marrow tolerance, which has been considerably extended by the availability of platelet concentrates and powerful broad spectrum antibiotics. In 1978 such an approach was introduced at St. Bartholomew's Hospital. In the light of there being no convincing evidence that maintenance therapy prolonged remission following very intensive initial treatment, and some (evidence) to the contrary [3, 9], it was decided to limit the duration of the programme to approximately 6 months by terminating all therapy after a maximum of six cycles of adriamycin (adria), cytosine arabinoside (araC) and 6-thioguanine (6-TG) given at approximately 3 weekly intervals.

Preliminary results were reported in April 1982 [1] and this report constitutes a follow-up of 98 patients under the age of sixty.

B. Materials and Methods

I. Patients

Ninety-eight consecutive patients aged 15–60 with newly diagnosed AML commenced treatment at St. Bartholomew's Hospital between April 1978 and November 1981 and form the basis of this report (Table 1).

Table 1. Pre-treatment clinical details; $n=98$
M : F 52 : 47

Blast count $\times 10^9$/litre		Platelet count $\times 10^9$/litre
Range	0 – 392	8 – 386
Mean	28	74
Median	5	42

F-A-B Classification

M	1	2	3	4	5	6	Total
	39	19	9	21	5	6	99

II. Treatment (Table 2)

Two combinations of adria, araC and 6-TG were employed sequentially between April 1978 and June 1980. The initial combination was the least intensive (B-IX) and modified in favour of the next (B-X) because inadequate aplasia was induced. This was abandoned because of unacceptable early mortality and B-IX re-instituted. The finding that the duration of remission was significantly longer in patients surviving to enter CR with B-X, and improvements in

Table 2. Details of treatment programmes

Drug	Dose (mg/m^2)	Days	Cycles
	B-IX		
Adriamycin	50	1	1+2
	50	1	3+4
	25	2	3+4
	50	1+2	5+6
Cytosine arabinoside	200	1–5	1–6
6-Thioguanine	200	1–5	1–6
	B-X		
Adriamycin	25	1, 2, 3	1–6
Cytosine arabinoside	200	1–7	1+2
		1–5	3–6
6-Thioguanine	200	1–7	1+2
		1–5	3–6
	B-Xb		

Doses of all three drugs the same as B-X; araC given by continous intravenous infusion; araC and 6-TG given for 7 days in all cycles

supportive care led to the introduction of an intensification of B-X to B-Xb.

The majority of patients treated between July 1980 and November 1981 received this modification of the B-X programme, whereby adria was given on the 1st and 2nd days (total dose 75 mg), araC was given by continuous intravenous infusion, and araC and 6-TG were continued for 7 days in all cycles. Four patients received adria on the first 2 days with araC at 100–150 mg/m^2 per day by continuous infusion for 10 days without 6-TG. AraC at a dose of 2 Gm/m^2 twice daily (given over 3 h) for 6 days was substituted for one consolidation course in three patients. For the purpose of this analysis, primarily concerned with determining whether there was an advantage in treating patients with chemotherapy including 7 days of araC as opposed to 5, all these patiens are considered together. A maximum of six cycles was prescribed over approximately 6 months, patients being observed subsequently without therapy prior to relapse. If an HLA identical donor was available, chemoradiotherapy followed by allogeneic bone marrow transplantation was performed (Dr. RL Powles) at the completion of chemotherapy. Such patients have been excluded from the analysis from the time of transplantation.

C. Results

Complete remission (CR) was achieved in 56/98 patients with the initial therapy and in a further three after the addition of high-dose araC to give an overall complete remission rate of 59/98 (60%) (Table 3). The reasons for failing to enter CR are shown in Table 4. No patient with a presenting blast cell count in excess of 100×10^9/liter entered CR.

Table 3. Frequency of complete remission

B-IX	B-X	B-XB	Total
30/37	11/27	18/34	59/98

B-IX vs B-X $P=0.01$; B-IX vs B-Xb $P=0.01$; B-X vs B-Xb n.s.

Table 4. Reasons for failure to achieve remission

	B-IX	B-X	B-Xb	Total
Resistant leukaemia	2	7	5	14
Fatal infection	1	3	6	10
Haemorrhagic death	3	3	1	7
Other	1	3	4	8
Withdrawn	–	–	3	3
Total	7	16	19	42

Table 5. Proportion of patients receiving total planned therapy

B-IX	B-X	B-XB
23/30	8/11	5/15

B-IX vs B-Xb $P=0.01$; B-X vs B-Xb $P=0.05$

Only 36/59 patients entering complete remission completed six cycles of therapy, the proportion being significantly lowest ($P<0.01$) for patients receiving the most intensive programme (B-Xb) (Table 5). Also the mean time to completion of three cycles of therapy was significantly longer for B-Xb (90 days) than B-IX (86 days, $P=0.01$) or B-X (75 days, $P=0.05$).

Twenty-one patients have continued in first unmaintained CR between 6 months and 4 years with a median follow-up of 18 months (Fig. 1). Thirty-eight have relapsed, one has died of septicaemia without re-

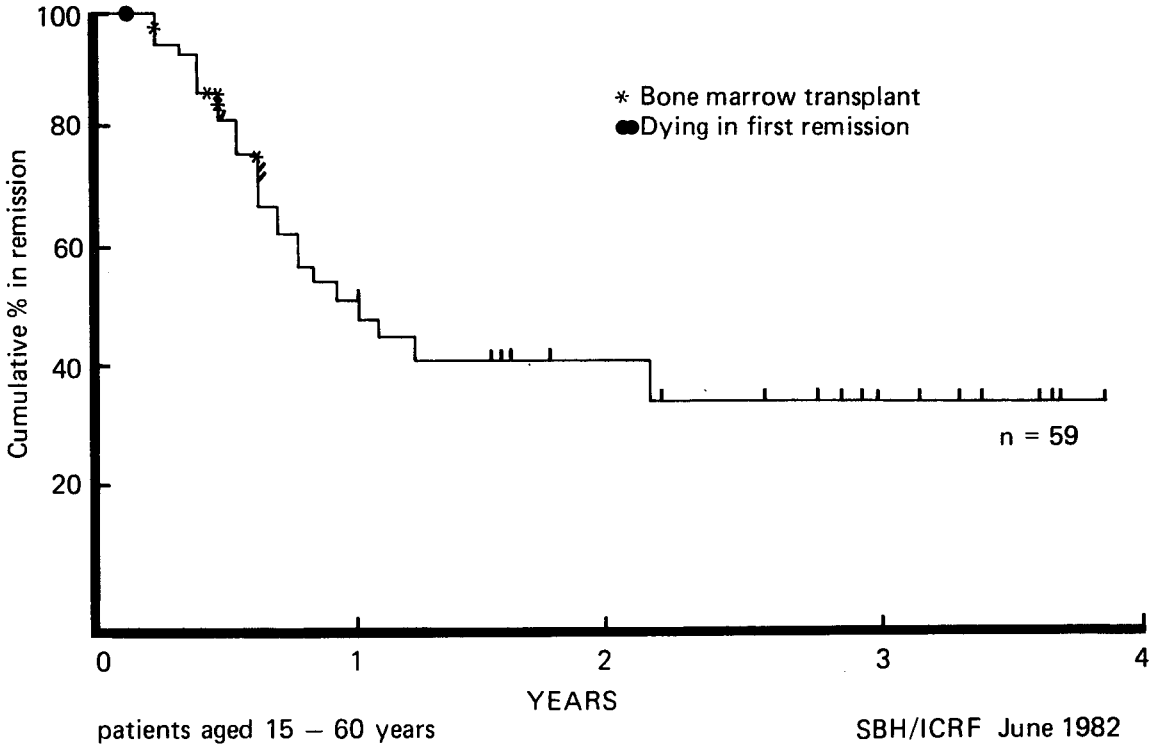

Fig. 1. Duration of first complete remission

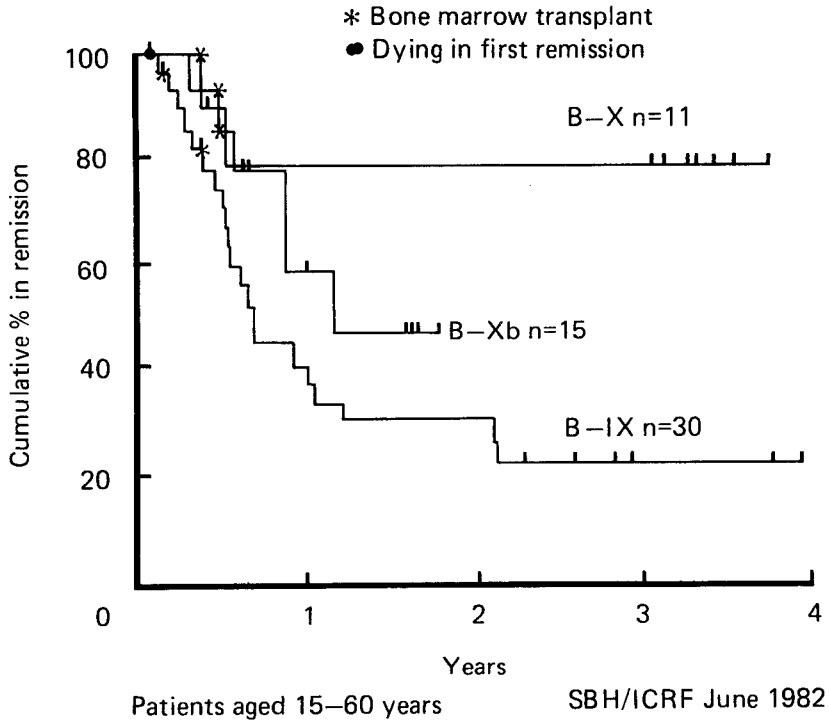

Fig. 2. Duration of first complete remission. Influence of treatment programme

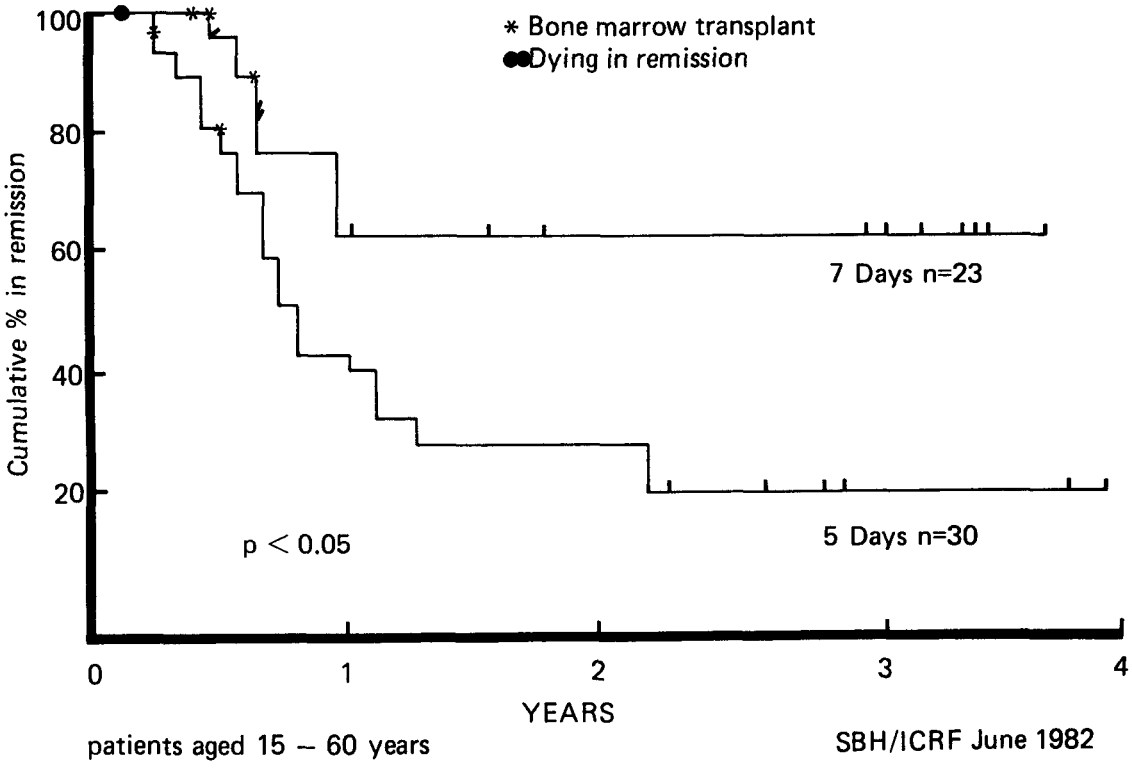

Fig. 3. Disease-free survival. Influence of initial therapy. araC: 7 days vs 5 days

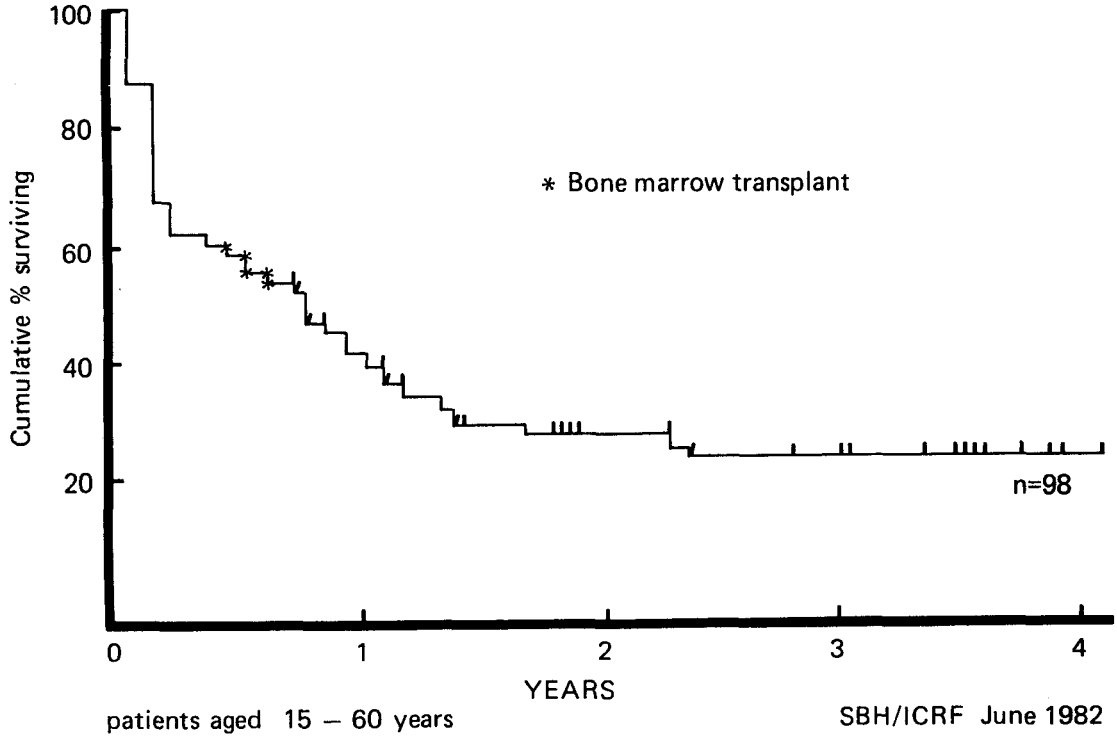

Fig. 4. Overall survival

lapse, and bone marrow transplantation was performed in five, all of whom have continued in remission but who have been excluded from the analysis from that time. The median duration of remission was 1 year. It was significantly longer for patients receiving B-X than those receiving either B-IX or B-Xb (not an entirely homogenous group) (Fig. 2). All three patients receiving B-Xb who proceeded to high-dose araC prior to entering complete remission have relapsed at 4, 8½ and 9 months. Compari-

son of the duration of remission of patients entering complete remission with a treatment programme contining 5 days araC and 50 mg/m² of adria in the first two cycles with those receiving one containing 7 days araC with 75 mg/m² of adria in divided doses reveals a significant advantage for the latter group ($P < 0.05$, Fig. 3)

The overall disease-free survival curve for all 98 patients commencing treatment in all of the studies in shown in Fig. 4.

D. Discussion

The complete remission rate for adults under 60 years of age treated at St. Bartholomew's Hospital has risen modestly from 43% (1974–1978) to 60% in the period 1978–1982, being highest in the group receiving the least intensive programme. Reducing the duration of therapy to approximately 6 months has not been associated with a reduction in the median duration of remission, nor in the proportion without relapse at 3 years. On the contrary, the current analysis shows a statistical advantage for patients receiving short-term therapy over those treated in previous studies at St. Bartholomew's Hospital. This is, however, the group treated most recently and obviously late relapses may occur. It is unlikely, however, that the results will be worse than those achieved previously, at least justifying the further investigation of short-term therapy. Comparison of the duration of remission attained with B-IX, X, and Xb shows an advantage for B-X over both the others in spite of the fact that B-Xb was nominally more intensive than B-X. There are several possible explanations for this. It may be that the very long remission duration of patients receiving B-X was a statistical fluke, in part a reflection of the small number of patients. Two other alternatives are possible. First, the premature termination of B-Xb prevented many patients receiving adequate therapy. Second, resistant leukaemia was allowed to develop by the prolonged intercycle time.

The fact that an advantage may be demonstrated for the 7 (or more) -day schedules, but not for those in which araC was given by continuous infusion, may be variously interpreted. It seems most likely that this paradoxical result is a reflection of the fact that 200 mg/m² araC when given by twice daily bolus injection for 7 days in combination with adria and 6-TG is just tolerable for six cycles at 3–4 weekly intervals, but intolerable when given by infusion. It may therefore be inferred that if the schedule of administration of choice is a 7-day continuous infusion, the daily dose of araC must be reduced, or the other drugs omitted.

None of these results demonstrates that there is no place for maintenance chemotherapy for AML, but the relapse-free pattern suggests that it may be superfluous for at least a proportion. The results of other studies also suggesting that the intensity of the initial and immediate post-remission therapy, whether chemotherapy or chemotherapy with radiotherapy and bone marrow transplantation, persuade us to pursue this direction of research.

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