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Acute Myeloid Leukaemia in Childhood: Treatment in the United Kingdom

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Childhood acute myeloid leukaemia (AML) is rare. The annual incidence rate, based on the Manchester Children's Tumour Register [1], is 5.1 cases per 10^6 children under 15 years of age, thus approximating 60–70 new cases per annum in the United Kingdom. At the Hospital for Sick Children, Gt. Ormond Street (HSC), an average of eight to ten new cases of AML are referred per annum.

A. Treatment Before 1975

Figure 1 shows the survival of all patients treated in two consecutive periods at the HSC. Before 1972 patients received a variety of drugs; between 1972 and 1975 daunorubicin and cytosine arabinoside (araC) were used in induction, CNS prophylaxis was given with intrathecal chemotherapy and treatment continued with 6-mercaptopurine or thioguanine for 2 years. There was no improvement in median survival but three patients remain in remission over 8 years from diagnosis.

B. The MRC UKAML Trial

Between 1975 and 1979 patients at the HSC were entered into the first Medical Research Council (MRC) trial for childhood myeloid leukaemia (UKAML). The design of this multicentre trial is shown in Fig. 2. Induction chemotherapy was followed by consolidation and CNS prophylaxis. At first patients were randomized to receive either no further treatment after consolidation, or immunotherapy. Immunotherapy consisted of BCG and irradiated allogeneic blast cells; one dose of 0.2 ml containing BCG and 2.5×10^7 blast cells was given intradermally each month for four doses. Subsequently a third arm was introduced, comprising 2 years maintenance chemotherapy with daily oral thioguanine and weekly subcutaneous araC.

I. Remission Induction

One hundred and fifty-eight patients were entered from centres throughout the United Kingdom. One hundred and five of these (66%) achieved remission after a median of three courses of chemotherapy. The cause of failure to achieve remission was analysed as suggested by Preisler [2]. Using his criteria 35 patients would be classified as class I or II failures who by implication might have benefited from more intensive chemotherapy. Early deaths (type V failures) accounted for 13 failures; six of these were associated with haemorrhage with or without disseminated intravascular coagulation, six with leucostasis and only one with infection.

Analysis of response to initial chemotherapy in relation to FAB class as de-

Table 1. UKAML response to induction according to FAB class

	M_1	M_2	M_3	M_4	M_5	M_6
No.	20	60	8	34	26	9
CR	13	46	2	25	17	1
Prop.	0.65	0.76	0.25	0.73	0.65	0.1

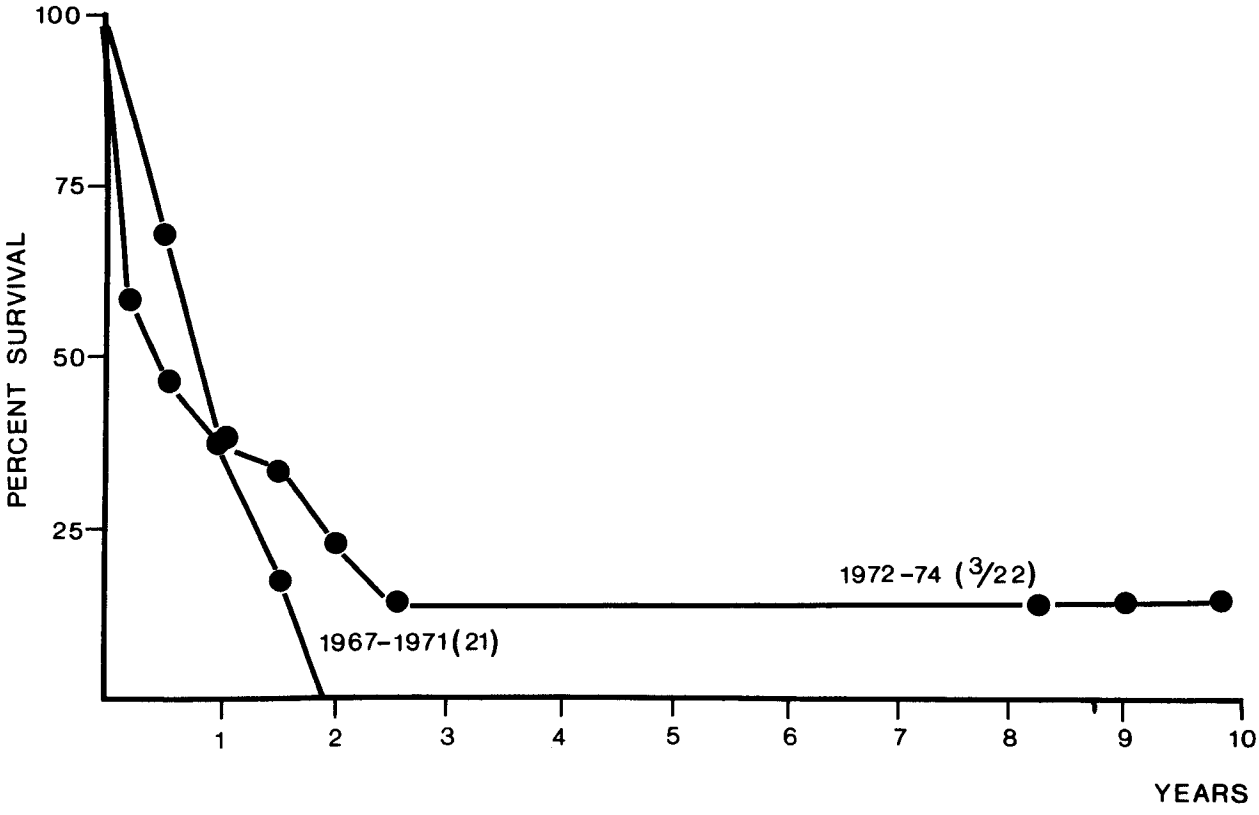

Fig. 1. Life table analysis of survival in children with AML treated in two consecutive periods at the HSC. Numbers in brackets indicate number still alive/total number

scribed by Bennett et al. [3] (Table 1) shows that the worse response is in M_3 AML, because of death from haemorrhage, and in M_6 AML because of failure to respond to chemotherapy. The deaths from leucostasis occurred in patients with M_4 and M_5 AML. The overall remission rate was lowest (52%) in patients with initial leucocyte counts in excess of 100×10^9/litre and highest (72%) in those with counts under 10×10^9/litre.

II. Consolidation

Consolidation chemotherapy comprised six courses of adriamycin, araC, thioguanine and vincristine and six doses of intrathecal araC. Cranial irradiation was not given. The overall incidence of CNS relapse was low with CNS relapse as a first event occurring in only three patients. Seventeen patients (11%) relapsed during this consolidation phase so that the overall number of patients available for randomization was 88 (56%). Four of these patients were not randomized, receiving transplantation or alternative chemotherapy, and have been withdrawn from subsequent analysis.

III. Further Treatment

The outcome in patients receiving no further therapy, immunotherapy and maintenance treatment is shown in Fig. 3. Although these results may appear to show

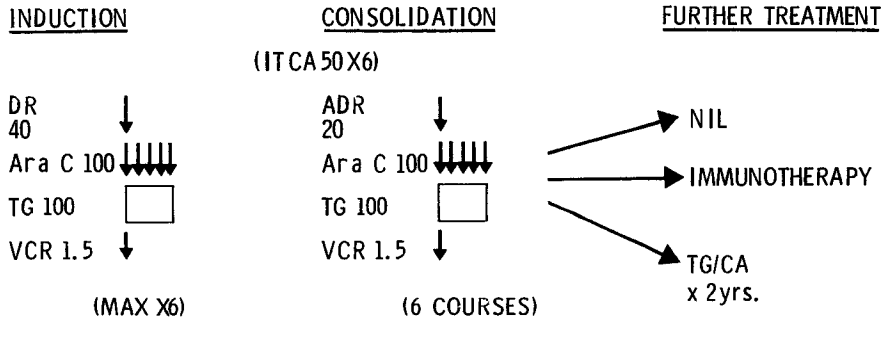

Fig. 2. Design of the MRC UKAML trial 1975–1979 (Drug dosages in mg/m² surface area)

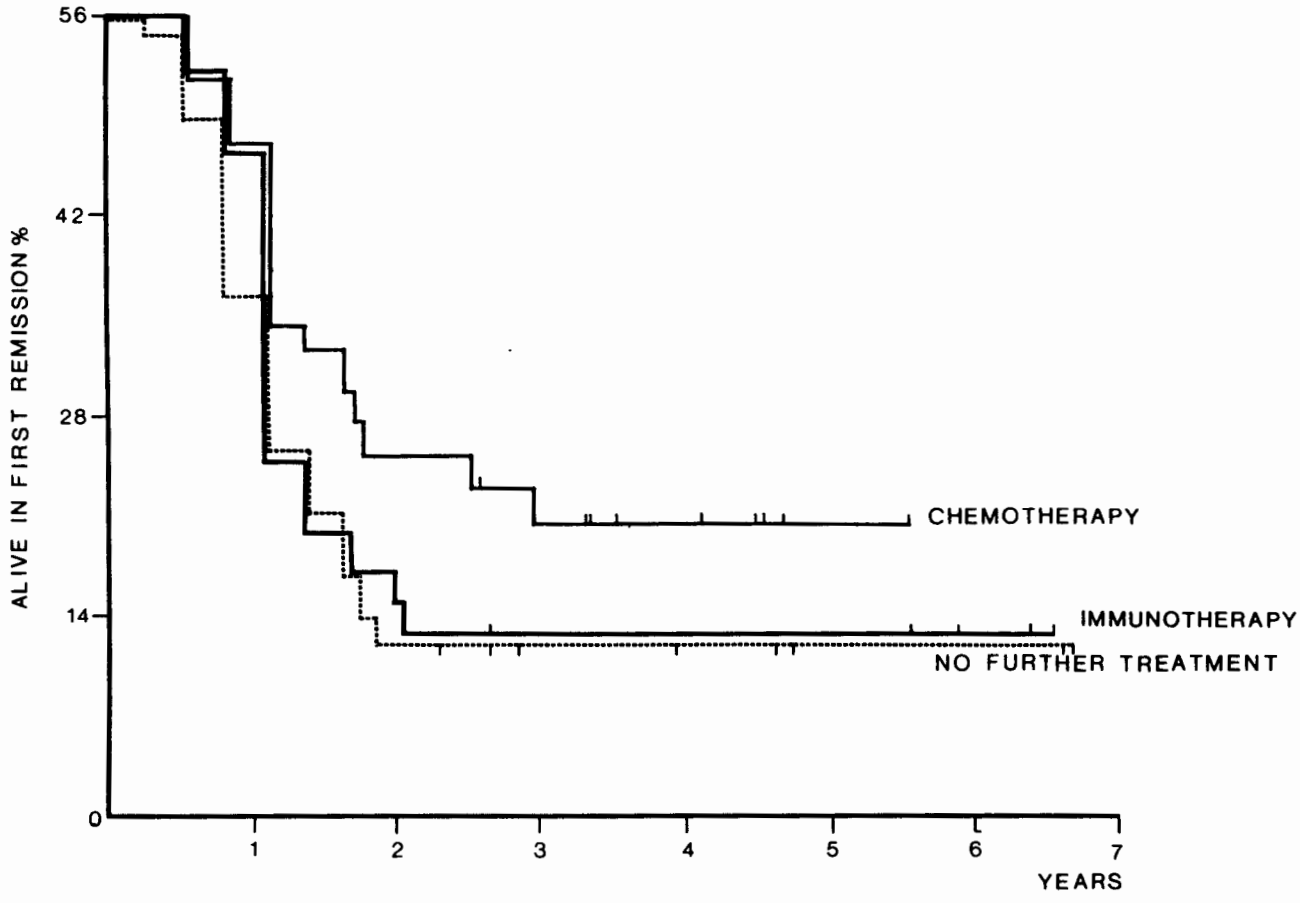

Fig. 3. MRC UKAML trial. Comparison of first remission duration in patients receiving chemotherapy, immunotherapy or no further treatment

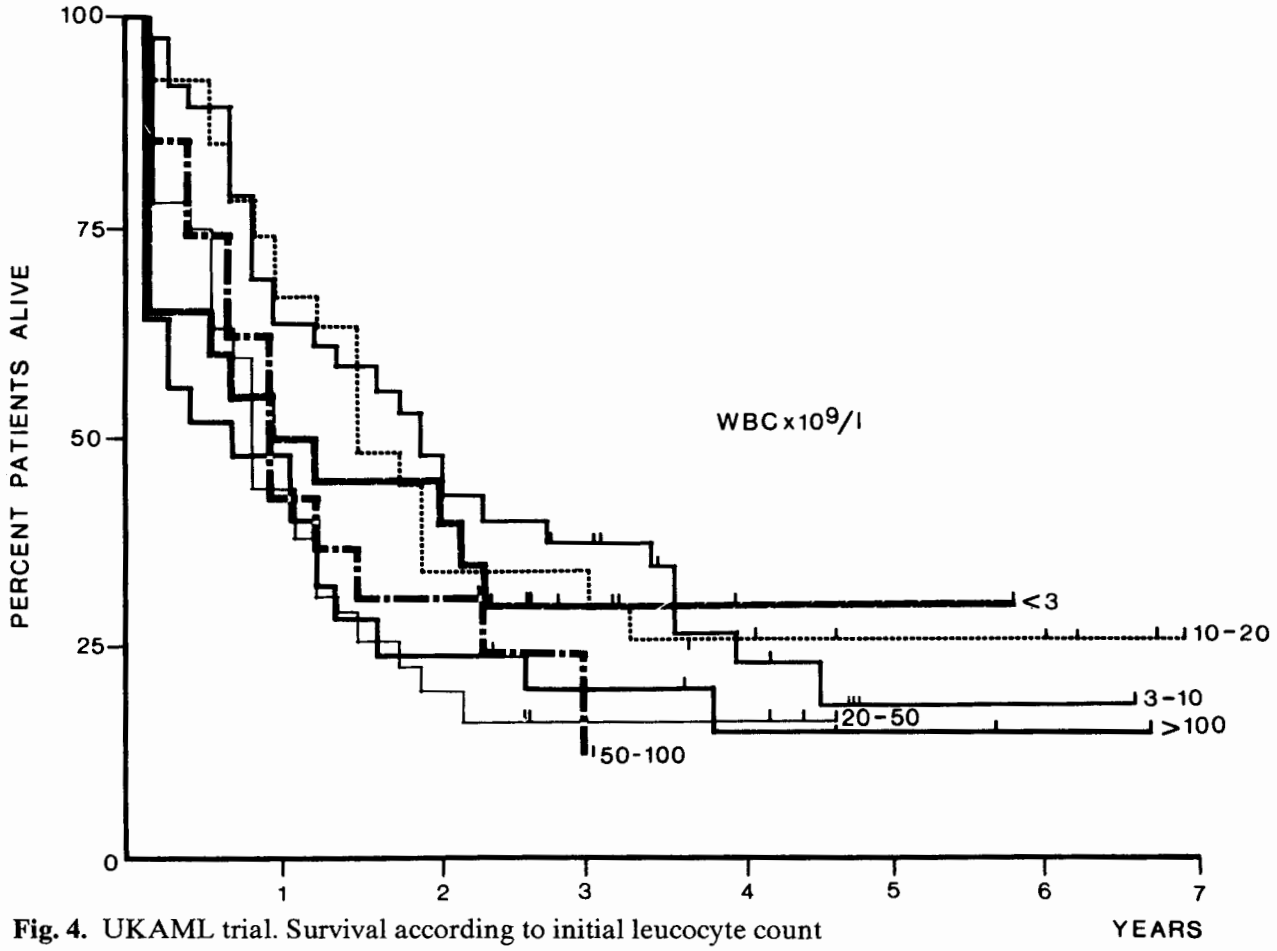

Fig. 4. UKAML trial. Survival according to initial leucocyte count

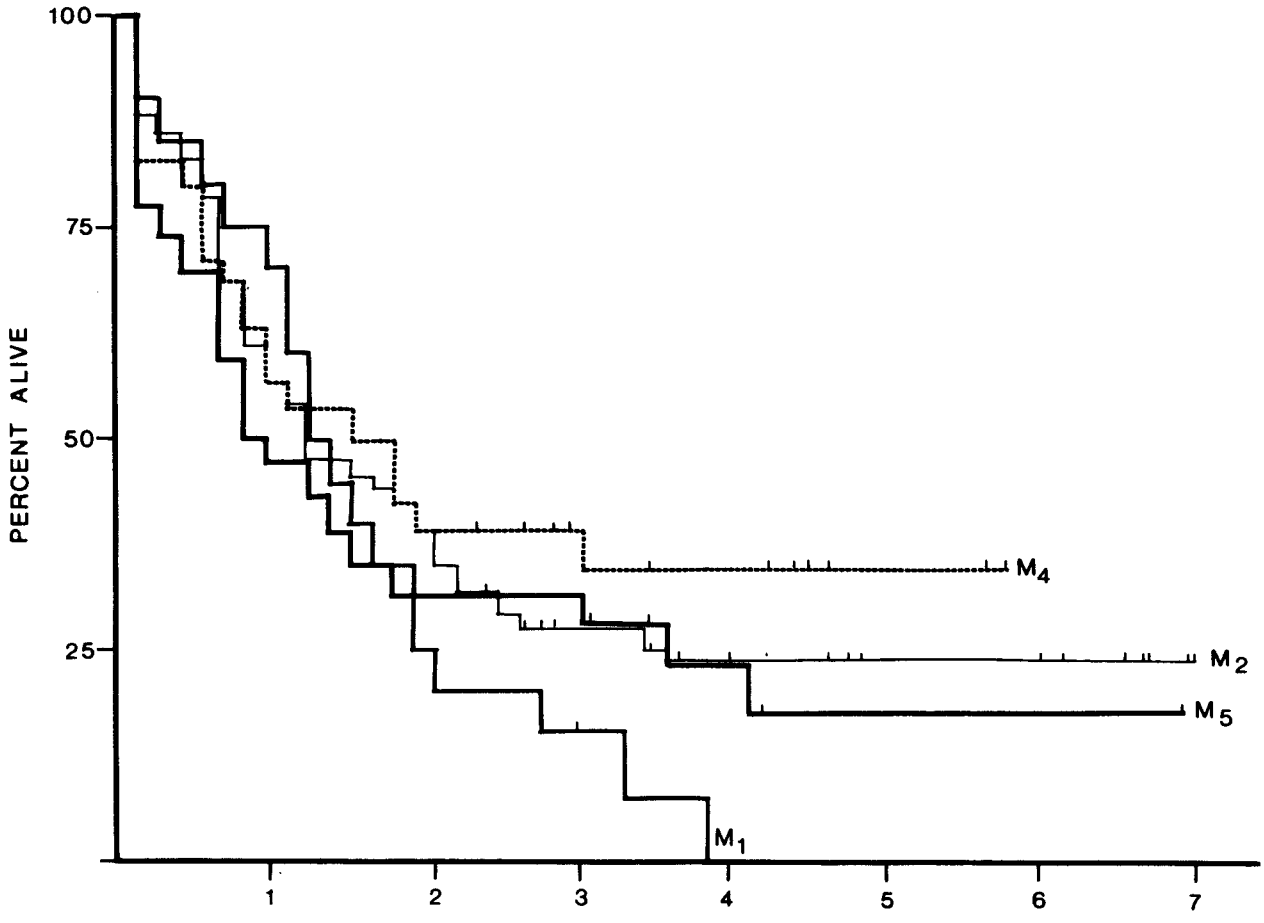

Fig. 5. UKAML trial. Survival according to FAB subtype

an overall advantage for chemotherapy, the comparison with patients randomized later does not show this effect and it appears that continued chemotherapy is at most of marginal benefit.

Analysis of results in terms of leucocyte count at presentation (Fig. 4) shows no consistent relationship but analysis of FAB class and survival (Fig. 5) suggests that patients with M_4 AML and M_2 AML may have a better prognosis than the other subtypes. There was no marked influence of age or sex on prognosis.

IV. Conclusions

This trial illustrates the difficulties arising in accruing patients with a rare disease for a randomized trial. In retrospect, as expected, immunotherapy proved of no benefit in maintaining disease-free survival and long-term chemotherapy was of marginal, if any, benefit.

V. Bone Marrow Transplantation (BMT) in First Remission

During the latter years of this trial BMT had become increasingly accepted as treatment for AML in first remission. A comparison of patients at the HSC with AML achieving stable remission and treated with chemotherapy compared with patients referred to the Royal Marsden Hospital for BMT in first remission has shown a clear benefit in favour of transplantation [4].

However, a major limitation of this form of treatment, in view of the small family size in the United Kingdom, is the limited number of patients with suitable donors. Less than one-quarter of children with AML seen at the HSC have HLA-DR identical donors.

C. The Eighth AML (Paediatric) Trial

Since there is little evidence that childhood AML is different from adult AML, from

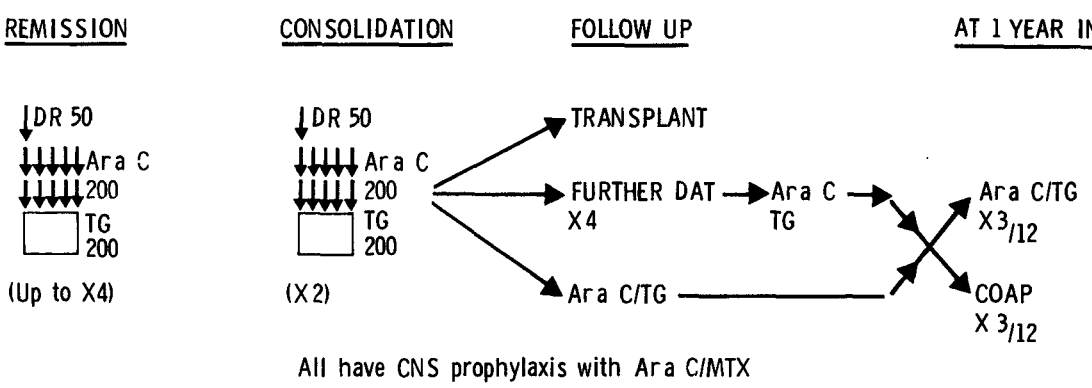

Fig. 6. Design of the MRC eighth AML (paediatric) trial opened May 1980

1980 onwards children have been entered into the ongoing MRC multicentre trial for adult AML. An outline of this protocol is given in Fig. 6. Remission induction is based on the DAT protocol described by Rees and his colleagues at Cambridge [5]. It might be expected that this more intensive regime with 12-hourly araC and thioguanine would produce a higher remission rate than seen in UKAML, and so far 79% of the 48 children entered have achieved remission. Patients in remission receive two further courses of DAT and are then randomized to further consolidation or to start maintenance. All receive chemotherapy for approximately 1 year. Patients with a suitable donor receive BMT in first remission, but so far only four patients have been transplanted.

D. Conclusions

The major obstacle to treatment of AML is bone marrow relapse. At present BMT is only available to the minority of patients with HLA-DR identical donors. It remains to be seen whether more intensive induction and consolidation will increase the proportion of patients achieving disease-free survival or whether developments in BMT will enable this form of treatment to be offered to a larger number of children.

Acknowledgements

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