

# **ACUTE MYELOID LEUKAEMIA IN CHILDREN**

## *(with results of the Medical Research Council MRC AML 10 TRIAL)*

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### **Introduction and Historical Perspective**

There have been a number of excellent recent reviews of the management of acute myeloid leukaemia (AML) in children<sup>(1-15)</sup> which deal adequately with the details of epidemiology, aetiology, molecular biology and historical results. It is not the intention of this review to reiterate known facts but rather to present the results of a very large trial which has recently been completed by the UK Medical UK Research Council and to address the current problems and future prospects.

AML is a rare disease in children, and within a country with a population of 50 million, one can expect to see about 50-70 new cases per year. One can thus immediately see that there is a problem in carrying out clinical trials which stand any chance of reliably detecting important differences between different treatment regimens. A review of the nine most important studies reported up to 1994<sup>(6-12)</sup> shows that more than half had recruited fewer than 200 children and only the US-CCG studies regularly recruit more than 300. In the future, we hope that there will be more of an international effort to improve the previously unsatisfactory results. At present we have chosen to join with our colleagues to perform trials covering the age range up to 60 years. There is in fact little scientific evidence in favour of a different biology for AML in childhood apart possibly from the 15% of those presenting below the age of 15 years who have high white cell count ( $> 100 \times 10^9/l$ ) and a tendency to monocytic forms of disease (Table 1). Another important association is that between Down's syndrome and megakaryoblastic leukaemia,<sup>(13,14)</sup> which is associated with a very good prognosis with chemotherapy alone.

**Table 1. Complete remission rates by presentation features**

Parameter	Value	No. of children	% of children	CR rate(%)	for difference p-value
All children	—	341	100	92	
Sex	Male	195	57	92	0.9
	Female	146	43	92	
Age (years)	0	25	7	92	0.8
	1-4	113	33	93	
	5-9	87	26	90	
	10-14	116	34	93	

Type of AML	<i>de novo</i>	321		94		93	0.07
	mds-AML	18		5		89	
	s-AML2		1		50		
FAB type	M0	5		1		100	0.01
	M1	57		17		96	
	M2	116		34		93	
	M3	27		8		100	
	M4	49		14		84	
	M5	43		13		95	
	M6	5		1		60	
	M7	21		6		95	
	RAEB-t	13		4		85	
	(unclassifiable/ not known	5		1		60)	
CNS involvement	No	317		93		92	0.4
	Yes	24	7		88		
Performance status	Well	182		53		95	0.005
	Ill	136		40		90	
	Very ill	23		7		78	
White blood count (x 10 <sup>9</sup> /l)	0-9	138		40		95	<0.000 1
	10-99	149		44		93	
	100-199	30		9		93	
	200+	22		6		68	
	(not known	2	1	—			
Cytogenetic group	Favourable	76		22		95	0.3
	Intermediate	160		47		91	
	Adverse	27		8		89	
	(not known	78		23		94)	

\* **Trend (ordinal and continuous variables) or heterogeneity (categorical variables) - unclassifiable and not known groups are not included in the statistical tests.**

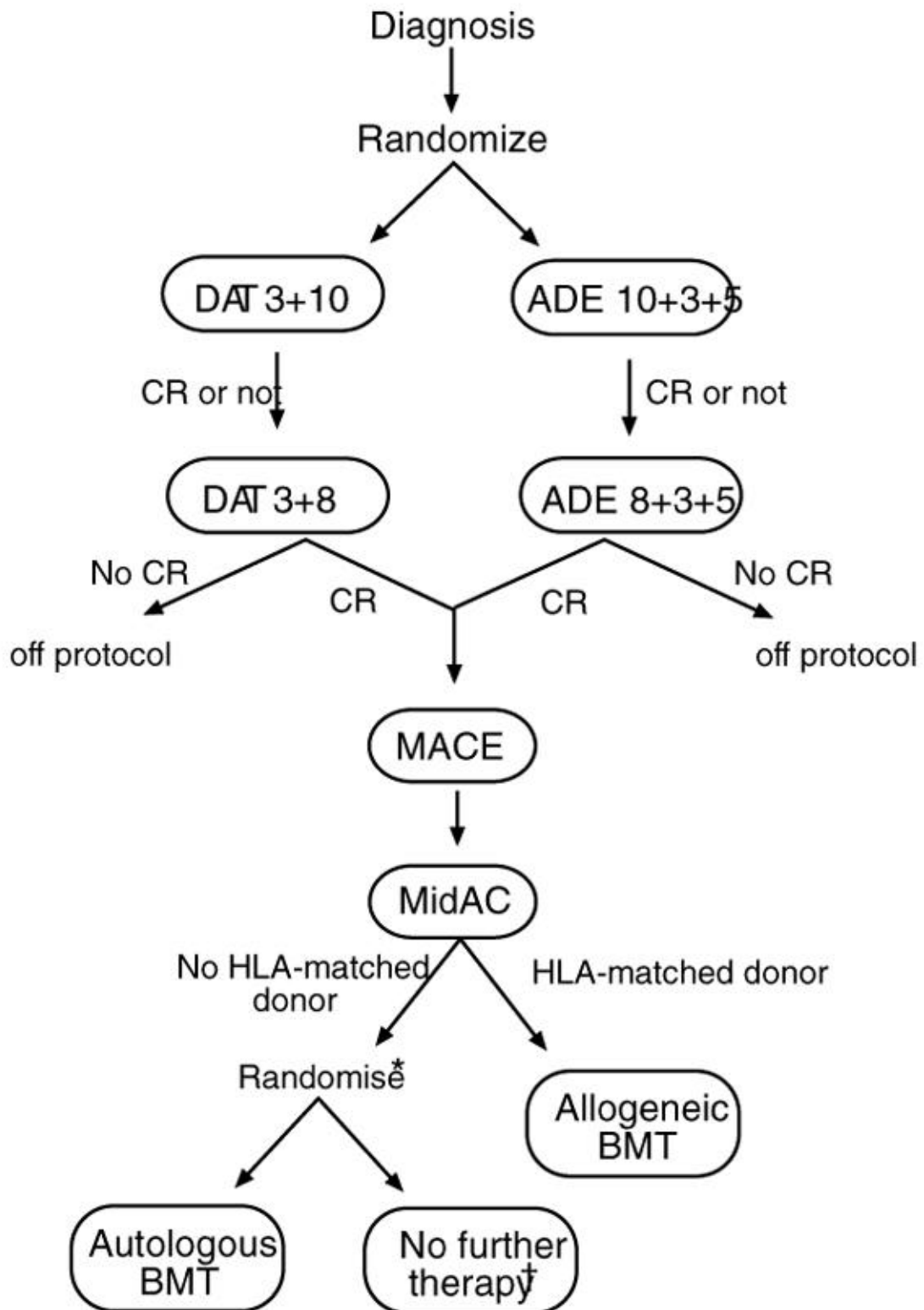
Although one could spend a great deal of time summarising the results of trials published up to 1994, it should suffice to say that complete remission rates varied between 77% and 85% within trials which took place during the last 15 years.<sup>(1)</sup> The majority of failures occurred due to resistant disease, but death during marrow aplasia occurred in between 5% and 13% of children entered into the trials. There is, however,

good evidence of an improvement in supportive care for these patients, which has allowed the use of much more intensive protocols.<sup>(15)</sup> The disease-free survival, which had historically been of the order of one-third or less in the 1970s, was reported in these more modern series as being between 31% and 61%, with the smaller trials often appearing to produce slightly better results.

### **The MRC AML 10 Trial**

Between May 1988 and April 1995, 364 children (aged 0-14 years) were entered into the AML 10 trial in 40 centres in the United Kingdom, Republic of Ireland and New Zealand. The rest of this abstract will explore the results of this trial, the lessons that have been learned and the questions which are still outstanding in the management of this very challenging disease.

# MRC-AML10: Protocol flow chart



**Figure 1. MRC-AML 10: Protocol flow chart.**

**\* Randomisation actually occurs before course 4**

**<sup>1</sup> Autologous BMT reserved for second remission therapy if relapse occurred.**

**Abbreviations: DAT = Daunorubicin, Cytarabine, 6-thioguanine; ADE = Daunorubicin, Cytarabine, Etoposide; MACE = Amsacrine, Cytarabine, Etoposide; MidAC = Mitozantrone, Cytarabine**

The trial had two randomisations (Figure 1): the first was to determine whether thioguanine (as part of DAT) or etoposide (as part of ADE) was preferable with regard to efficacy and toxicity in the initial two courses of chemotherapy. Patients who had an HLA-matched sibling donor (MSD) were scheduled for an allogeneic bone marrow transplant (BMT) after they had completed four courses of chemotherapy and were not eligible for second randomisation. The remainder, who did not receive MSD-BMT, were randomised to receive high-dose therapy with cyclophosphamide and total body irradiation (or busulphan-cyclophosphamide for the under 2-year olds) with autologous marrow rescue (autoBMT) or to receive no further therapy.

Another important aspect of the trial was to more clearly define the various demographic, laboratory and morphological subgroups of AML in children. In Table 1, the remission rates are also shown. It can be seen that there is a male preponderance (1.3:1 sex ratio) and a fairly even distribution of cases by age at diagnosis. There was a relative paucity of M0, M3 and M6 cases in childhood compared with adults, as has been previously recognised.<sup>(16)</sup> The table also clearly shows that age and sex had no influence on outcome with regard to remission rate. In this trial the only patients to receive cranial irradiation were those who had overt CNS disease at diagnosis. The other patients all received just five doses of intrathecal therapy, and the extremely low CNS relapse rate (less than 2%) testifies to the efficacy of this approach, which also has the advantage of lesser toxicity than cranial irradiation. Finally, patients with the highest white cell count ( $> 200 \times 10^9/l$ ), poor performance status, M4 myelomonocytic leukaemia or refractory anaemia with excess of blasts also have a slightly lower remission rate.

The DAT versus ADE randomisation was undertaken in 286 patients. There were no differences between the two regimens, which were equally efficacious in producing a very good remission rate of 91% (Table 2). Whether one used thioguanine or etoposide made no difference to outcome however one analyses the cases. In addition there was no difference in response to the two regimens within the monocytic varieties of AML (FAB M4 and M5). This helps to put to rest the old medical aphorism that monocytic varieties of leukaemia respond better to epipodophyllotoxins than to other chemotherapeutic agents.

**Table 2. AML10 Children - DAT vs ADE**

Endpoint	Treatment		Total	p-value (DAT vs ADE)	(Non-rand)
	DAT	ADE			

Number of patients	143	143	286		55
CR rate (%)	89	93	91	0.3	98
Induction death(%)	6	3	5		2
Resistant disease (%)	6	3	5		0
DFS (% at 5 yrs)	53	52	53	0.4	56
Relapse risk (% at 5 yrs)	43	39	41	0.9	39
Deaths in CR during consolidation (%)	5	8	7	0.2	6
Deaths in CR post BMT (%)	2	5	3	0.3	2
Survival from 28 relapse(% at 2 yrs)	15		22	0.7	28
Survival from 60 entry(% at 5 yrs)	53		56	0.3	67
EFI (% at 5 yrs)	47	49	48	0.6	54

**\*GOS and RMH (18 further non-randomised patients at other centres).**

The role of BMT in the management of AML is a point of contention. The severe late effects of transplant procedures, which involve high-dose therapy with or without radiotherapy, are well documented.<sup>(17)</sup> The MRC AML 10 trial attempted to elucidate the efficacy of these procedures (Table 3). Neither matched allografts nor auto-BMT improved survival, the apparent benefit for transplant in reduction of relapse risk being negated by higher procedure-related mortality after allogenic BMT and a better survival from relapse after auto-BMT in the previously non-grafted patients. There is no evidence at the present time that BMT has a role to play in any of the sub-groups of AML, but this position may change with better supportive care (e.g., prevention or treatment of graft-versus-host disease) or the possible enhancement of the antileukaemic effect of BMT by more intensive preparative regimens or the use of unrelated donors. It seems likely that

the small additional anti-leukaemic effect of auto-BMT may be reproduced by extra, but less toxic chemotherapy, and this is being investigated in the current MRC AML12 trials.

**Table 3. AML 10 Children - BMT**

Endpoint	A-BMT	Autograft Rando- misation Stop	p-value	Donor
Number	50	50		85
Number of BMTs	44(88%)	0		62 (73%)
Survival (% at 5 yrs)*	70	64	0.6	68
DFS (% at 5 yrs)*	70	50	0.06	60
Relapse risk (% at 5 yrs)*	29	50	0.04	30
Deaths in CR (%)*	2	0	-	13
Death in CR post BMT (%)	0	0	-	9 (13% of those receiving Allo-BMT)
Survival from 14 relapse	35		0.04	20
Endpoint	No donor	Allograft	p-value	
Number	230			
Number of BMTs	60 (A-BMT) 4 (MUD) 1 (mismatched)			
Survival (% at 5 yrs)*	63		0.6	
DFS (% at 5 yrs)*	52		0.2	

Relapse risk (% at 5 yrs)*	44	0.02
Deaths in CR (%)*	7	0.1
Death in CR post BMT (%)	1	0.0006
Survival from 25 relapse		0.5

\* from randomisation for Autograft, from CR for Allograft.

**Table 4. AML10 Children - Risk groups**

Endpoint	Good	Risk group Standard	Poor	Not known	p- value*	
Number of patients	75	157	29	70		
Survival from CR (% at 5 yrs)	82	60	22	64	<0.0001	
DFS (% at 5 yrs)	55	57	25	53	0.004	
Relapse risk (% at 5 yrs)	39	37	72	3	8	0.002
Deaths in CR (%)	9	9	10	11	0.8	
Survival from 70 relapse(% at 2 yrs)	14	0		23	<0.0001	

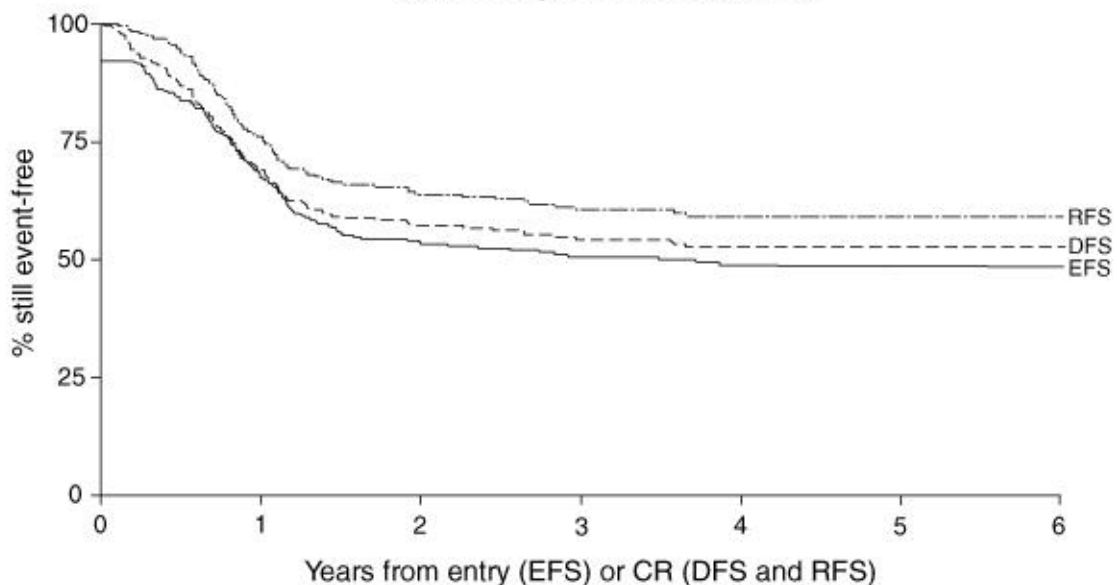
\* trend: good, standard, poor

**Definitions:** **Good** = favourable cytogenetics t(8;21),t(15;17),inv(16)  
**Standard** = not good or poor risk - i.e. neither favourable cytogenetics nor resistant disease  
**Poor** = resistant disease - >20% bone marrow blasts - after course 1 (and not favourable cytogenetics)

Now that we are at last curing a significant proportion of children with AML (see Figure 2 for results of the AML 10 trial), it is proving possible to define groups of patients who have a better or worse prognosis. The risk groups identified by the MRC AML 10 trial (including adult patients) are shown in Table 4. It can be seen that three groups of patients labelled good, standard and poor include 29%, 60%, and 11% of the

patients respectively, who have an 82%, 60% and 22% chance of survival at five years from remission. The poorest risk group in children consists mainly of those who have cytogenetic abnormalities involving chromosomes 7 and 5 and who frequently do not achieve CR after one course. This latter group obviously provides the greatest challenge with regard to cure, and most groups are investigating the use of therapeutic protocols such as the FLAG regimen (fludarabine, cytarabine and granulocyte colony-stimulating factor) and CLASP (high dose cytarabine timed sequential therapy along with asparaginase). Whether or not allogeneic BMT (MSD or unrelated donors) has a therapeutic role in this group of patients is still under investigation.

### AML 10 - Event-free survival, disease-free survival and relapse-free survival



**Figure 2. AML 10: Event-free survival, disease-free survival and relapse-free survival. The event-free survival at 6 years is 49%, the disease-free survival is 53% and relapse-free survival is 59%.**

The treatment of relapsed AML is highly unsatisfactory at present, with only about one in ten patients from the standard and poor risk groups surviving to two years from the point of relapse. We and others are exploring the use of unrelated donor transplants and auto-BMT (from marrow harvested during first remission) in these patients. We are also evaluating the use of MSD-BMT in second remission for good risk patients, when a donor is available. This latter strategy should reduce the exposure to the toxic effects of BMT for the nearly two-thirds of good risk patients who do not relapse.

Until recent years, few children with AML survived, and our knowledge of their ultimate state of health is lacking in many areas. We do know<sup>(18)</sup> that a significant proportion will suffer ototoxicity presumably due to the recurrent use of nephrotoxic drugs such as amphotericin B, aminoglycosides, etc. We must thus explore new avenues for prevention of this problem, such as the use of lipid amphotericin preparations and of single daily dosing of aminoglycosides. The biggest current worry for all groups of patients is the cardiotoxicity of anthracyclines,<sup>(19)</sup> cyclophosphamide and total body irradiation. We intend to reduce the use of BMT, explore the use of cardioprotectant

agents and investigate the use of regimens such as CLASP and FLAG, which do not contain anthracyclines, in pursuit of the goal of cure at least cost.

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