



7th South African Symposium on Haematopoietic Stem Cell Transplantation

MUD SCT for Paediatric AML?

Alan Davidson

Haematology / Oncology Service

Red Cross Children's Hospital



THE SCENARIO

- A 10 year old boy with M2 acute myelogenous leukaemia presents with a leukocyte count of $16 \times 10^9/L$
 - 30% myeloblasts (CD34+, DLA-DR+, CD33+, CD13+, CD7+)
 - normal male karyotype
 - 46 XY cytogenetics
 - CSF clear
- He achieves remission after induction chemotherapy
- He does not have siblings but the local registry indicated that there are several 10/10 matches available
- Do we transplant?

TWO QUESTIONS

■ ONE

Is transplant superior to chemotherapy alone? For which patients?

■ TWO

In the absence of a matched sibling donor, do we use a MUD?

THE EXPERTS IN A NUTSHELL

- In a series of articles in *BJH* in 2002 comparing MSD to chemotherapy:
 - Statistician ... need more data
 - Creutzig (BFM) ... good risk: no / high risk: yes
 - Burnett (adult transplanter) ... good risk: no / need to capitalise on reduction in relapse risk by improving transplantation effectiveness
 - Chen (CCG) ... ONLY t(8;21) and inv16 warrant *allo vs chemo* trial and that alternative donor SCT for poor risk patients may be warranted

Creutzig et al, **BJH** 2002;118:365-377

Wheatley et al, **BJH** 2002;118:351-356

Burnett et al, **BJH** 2002;118:357-364

Chen et al, **BJH** 2002;118:378-384

SO WHERE'S THE RCT?

- Problems with evaluating the “transplant arm” of a RCT
 - Patients in the transplant arm need to stay in CR long enough to be transplanted
 - Eligible patients may be unsuitable for medical or social reasons
 - Eligible patients may not have a donor
 - Those who do have donors may be better risk patients
- So the best tool we have is to compare those with and without donors
 - ... *genetic or Mendelian randomisation*
- Most studies show that the lower relapse rate after allogeneic transplantation is offset by more treatment related mortality
- IN PRINCIPLE transplantation should be offered to those with poorer response to chemotherapy and a higher relapse rate (poor risk disease)

CURRENT PAEDIATRIC PRACTICE

- Who is Doing What?
 - BFM
 - MRC
 - CCG, POG, COG
 - Others

- How are the patients faring?
 - Risk assignment
 - Treatment
 - Outcomes

THE BFM (studies 83/87/93)

■ STANDARD RISK

- M1 or 2 with Auer rods / M3 / M4_{eo}
- Cytogenetics t(8;21), inv16, t(15;17)
- < 5% blasts on day 15 marrow

■ HIGH RISK

- Other Morphology or Cytogenetics
- Non-remitters

⇒ TREATMENT STRATEGY

- Transplant for HIGH RISK only ... any matched related donor

THE BFM (studies 83/87/93)

- Results support the risk stratification, including the assignment of favourable morphology without favourable cytogenetics as good risk ...

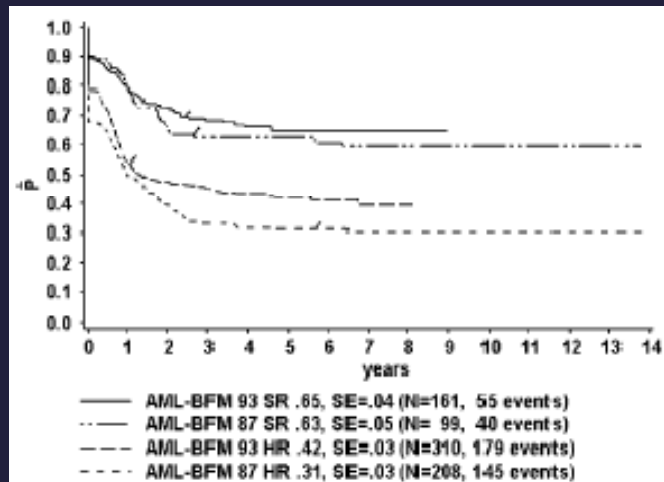


Figure 7 Comparison between the estimated probability of event-free survival in standard and high-risk patients in trial AML-BFM 93 and trial AML-BFM 87, 5-year data given (slash: see Figure 4).

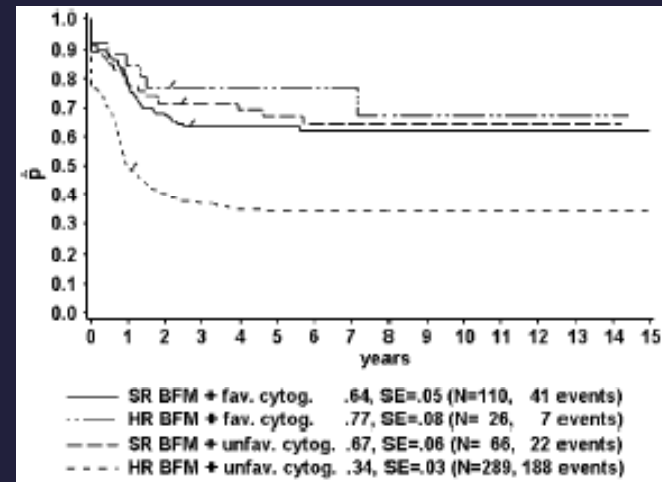


Figure 9 Estimated probability of event-free survival in patients with standard and high risk combined with favourable (fav.) or unfavourable (unfav.) cytogenetics, 5-year data given (slash: see Figure 4).

- BUT: Analysis of BFM-93 high risk patients showed no advantage of BMT over chemo alone

MRC AML (studies 10 and 12)

- GOOD RISK
 - t(8;21), inv16, t(15;17) or FAB M3 morphology
 - < 5% blasts on day 15 marrow

- STANDARD RISK
 - All others

- POOR RISK
 - Monosomy 5 or 7, del(5q), abn(3q), MAKA
 - > 15% blasts on day 15 marrow
 - *Presence of FLT3-ITD+ regarded as a poor prognostic factor (FLT3-inhibitor randomisation in adults)*

MRC AML (studies 10 and 12)

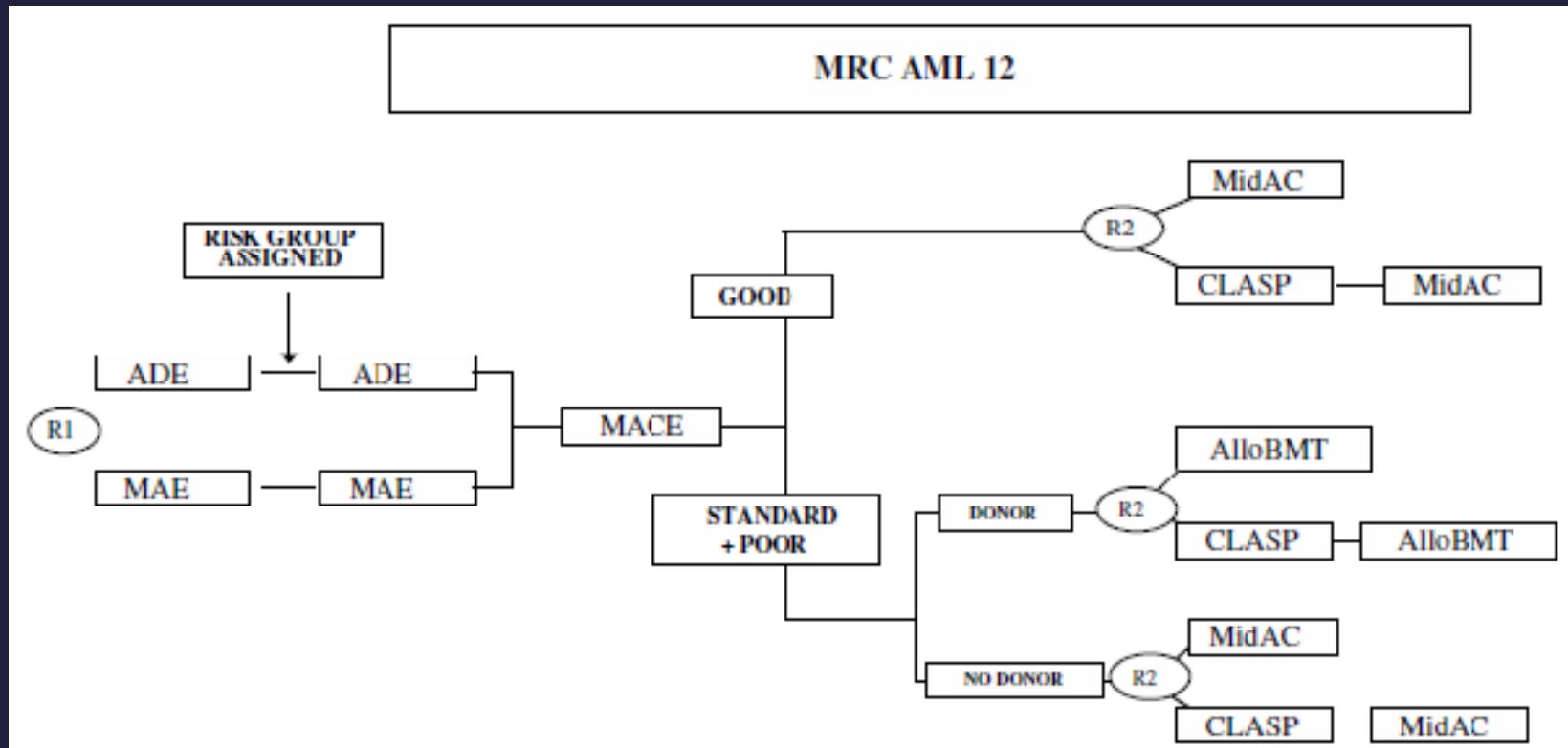
■ RESULTS BY RISK CATEGORY:

	AML 10		AML 12	
	Number	5yr OS%	Number	5yr OS%
■ GOOD RISK	85	79	84	
■ STANDARD RISK	127	60	76	
■ POOR RISK	49	25	47	

■ These results affected transplant decision-making thus ...

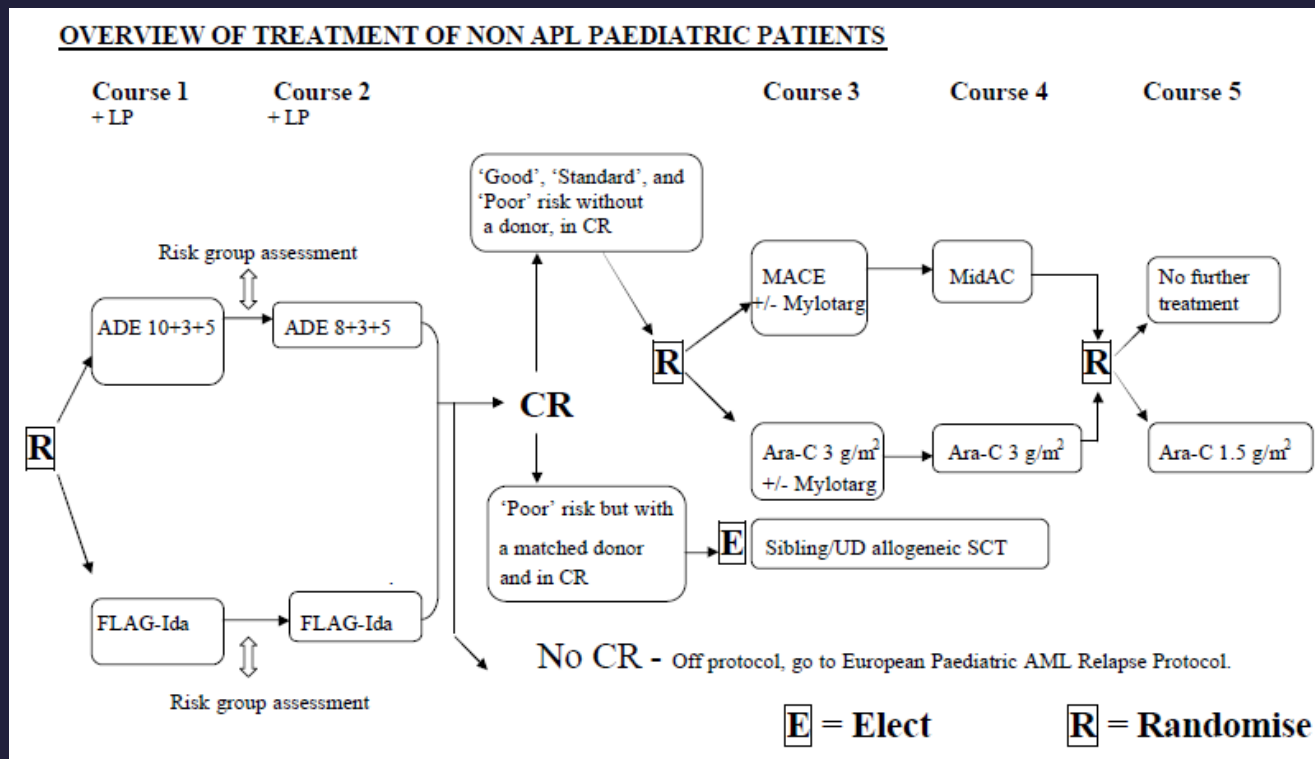
MRC AML 12

- MSD SCT randomisation (Donor/No-donor) for Standard and Poor Risk



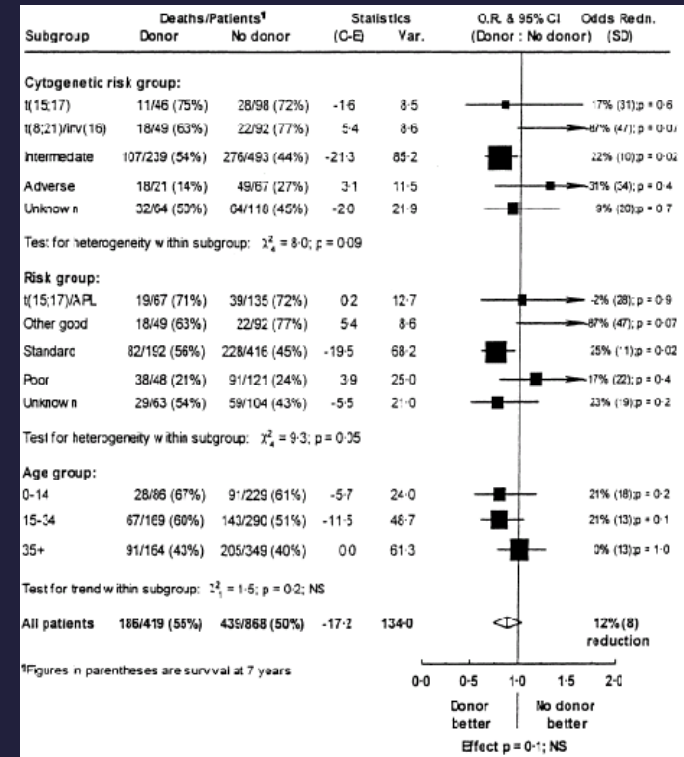
MRC AML 15

- MSD SCT randomisation (Donor/No-donor) for Poor Risk ONLY



MRC AML 10 – TRANSPLANT RESULTS

- Review of transplant in CR1 ...
- Powerful antileukaemic effect offset by
 - TRM
 - Better salvage rate after chemo only
- NO survival advantage to BMT in children



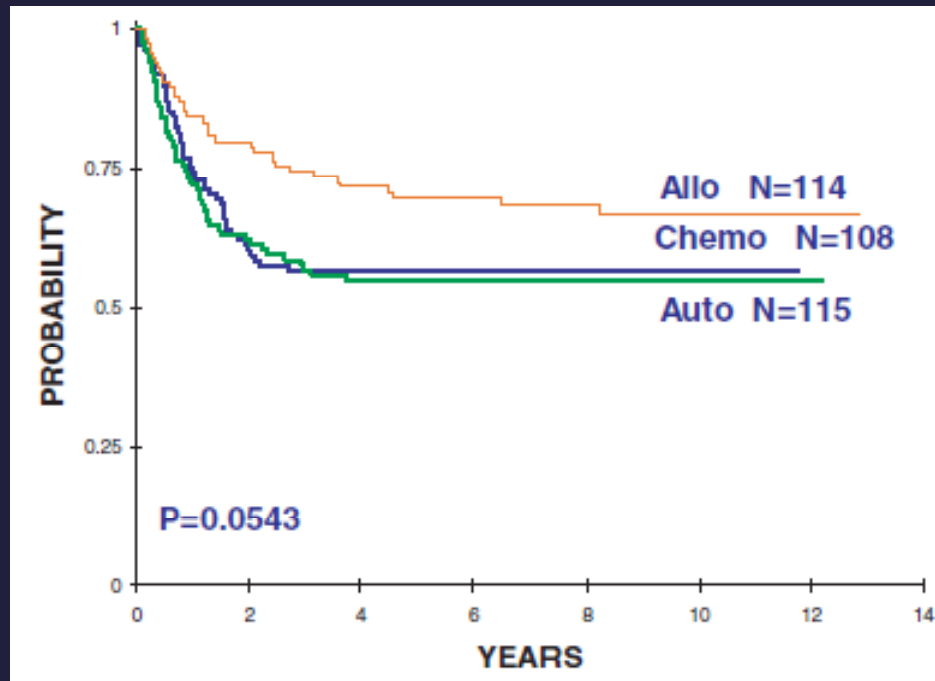
US CCG TRIALS

- Americans took an entirely different approach:
- All children with AML (excluding APL) in first remission with a MSD were transplanted ...

Table 1 Sequential CCG studies of AML

Study	251	213	2861	2891	2941
Years	1979–1983	1985–1989	1988–1989	1989–1995	1995–1996
N	355	355	84	617	53
Induction therapy	'7+3' (C+R)	'7+3' (C+R) vs DCTER ('Denver')	DCTER (IT)	DCTER IT vs ST N = 398 ^a N = 209 ^a	Ida-DCTER (IT) vs Ida-CTER (IT)
Consolidation/maintenance Chemotherapy	8 – drug cyclic (Aza, C, Car, MP, MTX, P, V, T) vs 5 – drug cyclic (Aza, C, CTX, V, T)	HDC ±5 – drug cyclic (Aza, C, CTX, V, T)		HDC	HDC ^b
Stem cell transplant	Allo CTX SD TBI	Allo CTX FTBI	Allo or auto BU/CTX	Allo or auto BU/CTX	Allo BU/CTX
GVHD prophylaxis	MTX	CSA, SCMTX	MTX	MTX	MTX

US CCG TRIALS



- Results showed superior survival for Donor vs No donor with the exception of children with inversion 16
- BUT on the strength of MRC data current COG trials are not transplanting children with inv 16 or t(8;21) in CR1

WHAT ABOUT OTHER GROUPS?

- France, Italy, the Netherlands, the Nordic countries ...
- Generally transplant non-APL AML with MSD in CR1
- Only the Italians claim better long term OS for Allo over Auto or Chemo alone
- A single centre in Spain reports excellent results using BFM based chemotherapy induction, and then transplanting all poor risk patients in CR1 (either by auto or allo) ... they showed an OS of 73% for this group ...
 - Toxic deaths were only 5.9% for allos and 3.2% for autos

AND WHEN WE POOL THE DATA?

- Combined data from POG, CCG and the MRC comparing MSD SCT to chemotherapy alone for paediatric AML in CR1:
 - 1373 patients
 - Better OS for those receiving BMT (62% vs 51%)
 - Better OS for the standard risk group only (58% vs 39%) where the risk of relapse was greatly reduced

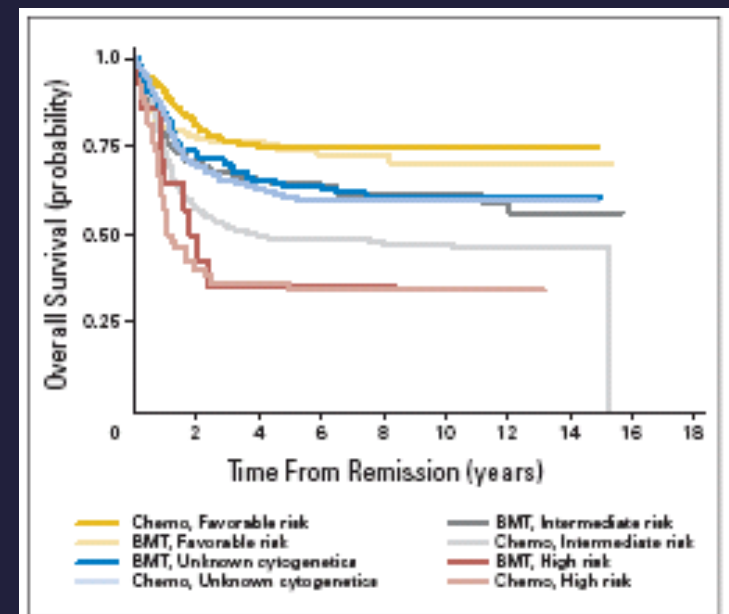


Fig 1. Estimated overall survival stratified by risk group and postremission treatment. Chemo, chemotherapy; BMT, bone marrow transplantation.

Woods et al, **Blood** 2001;97:56-62

Horan et al, **J Clinical Oncology** 2008;26:5797-5801

AND WHEN WE POOL THE DATA?

- This has been reiterated in a recent article in PBC ...

TABLE I. Controlled Comparisons of Allogeneic BMT Versus Other Postremission Modalities in Childhood AML

Group, year	N	Allo outcome (%)	Auto outcome (%)	Chemo outcome (%)	Comment
CCG 79-83	341 (90%)	47		34	Surv at 8 years $P < 0.05$
CCG 85-89	411 (94%)	52		46	Surv at 5 years $P = 0.13$
AEIOP 87-90	96 (76%)	51	21	27	DFS at 5 years $P = 0.03$
POG 88-93	321 (58%)	52	38	36	DFS at 3 years $P = 0.01/0.06$ Surv $P = 0.007/0.15$
UKCCG 88-95	315 (NA)	70		60	Surv at 7 years (time adjusted) $P = 0.10$
CCG 89-94	537 (82%)	60	48	53	Surv at 8 years $P = 0.002/0.05$

AND PAEDIATRIC META-ANALYSIS?

Paediatric Meta-analysis ...

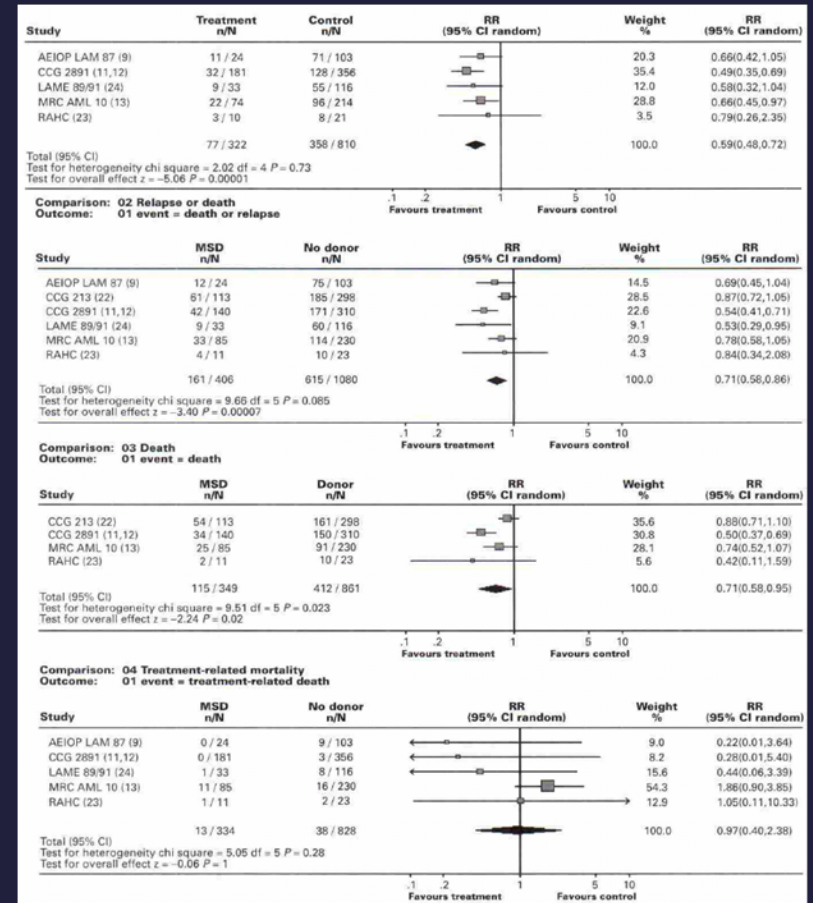
- Patients < 21 years from 1985 to 2000
- AML in CR1
- Donor / No donor studies (6) or RCTs comparing Auto to Chemo (4)

Conclusions ...

- AlloBMT reduces relapse (by 18%)
- AlloBMT improves OS (by 15%)

They commented:

“Difference between MRC-10 and the others is the increased TRM”



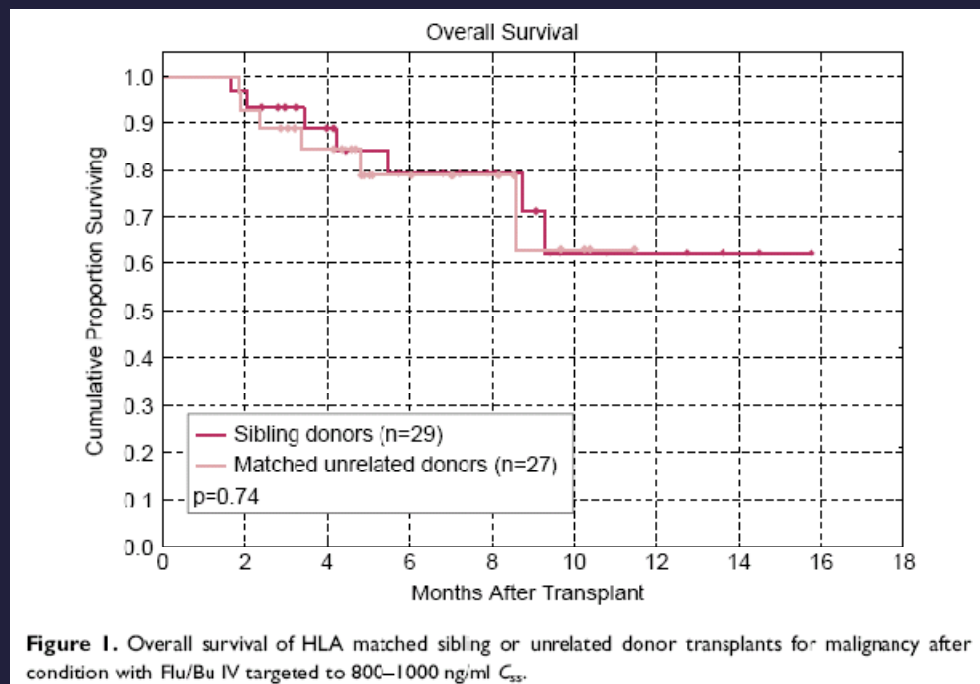
WHAT ABOUT MUD ALLO SCT

ARE WE GETTING BETTER AT IT?

- Italian adult study of 1180 consecutive leukaemia and lymphoma patients receiving Allo SCT over FOUR time periods ... starting before 1990 and ending in 2002.
- Despite [1] increasing patient age
 - [2] more unrelated transplants (alternative donors 3.5% to 50%)
 - [3] patients with more advanced disease
 - TRM in SCT post CR1 decreased: 34%, 25%, 21%, 6%
 - TRM in SCT post CR2 was little changed: 37%, 35%, 30%, 25%
- So we are getting better at Allo SCT and unrelated transplantation!
- SUPPORTED BY CIBMTR DATA SHOWN YESTERDAY! (*Apperley*)

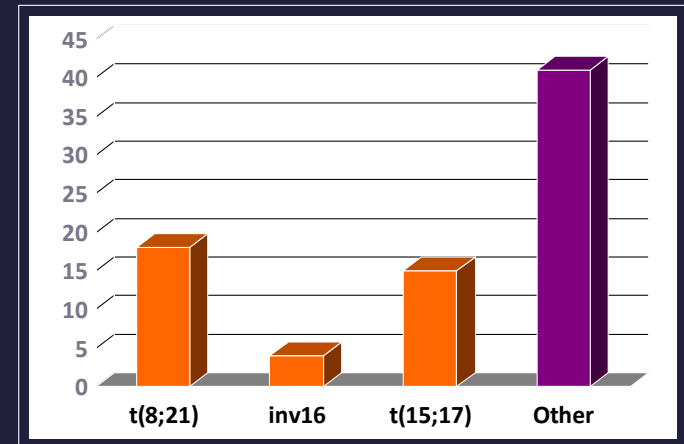
AND MUD SCT IN CR1 ... ARE WE JUSTIFIED?

- US adult review cites as reasons for improvement of MUD SCT ...
 - More precise HLA donor matching
 - Safer myeloablation (substituting fludarabine for one of the alkylators)
- Describing a cohort of 56 adult patients ...



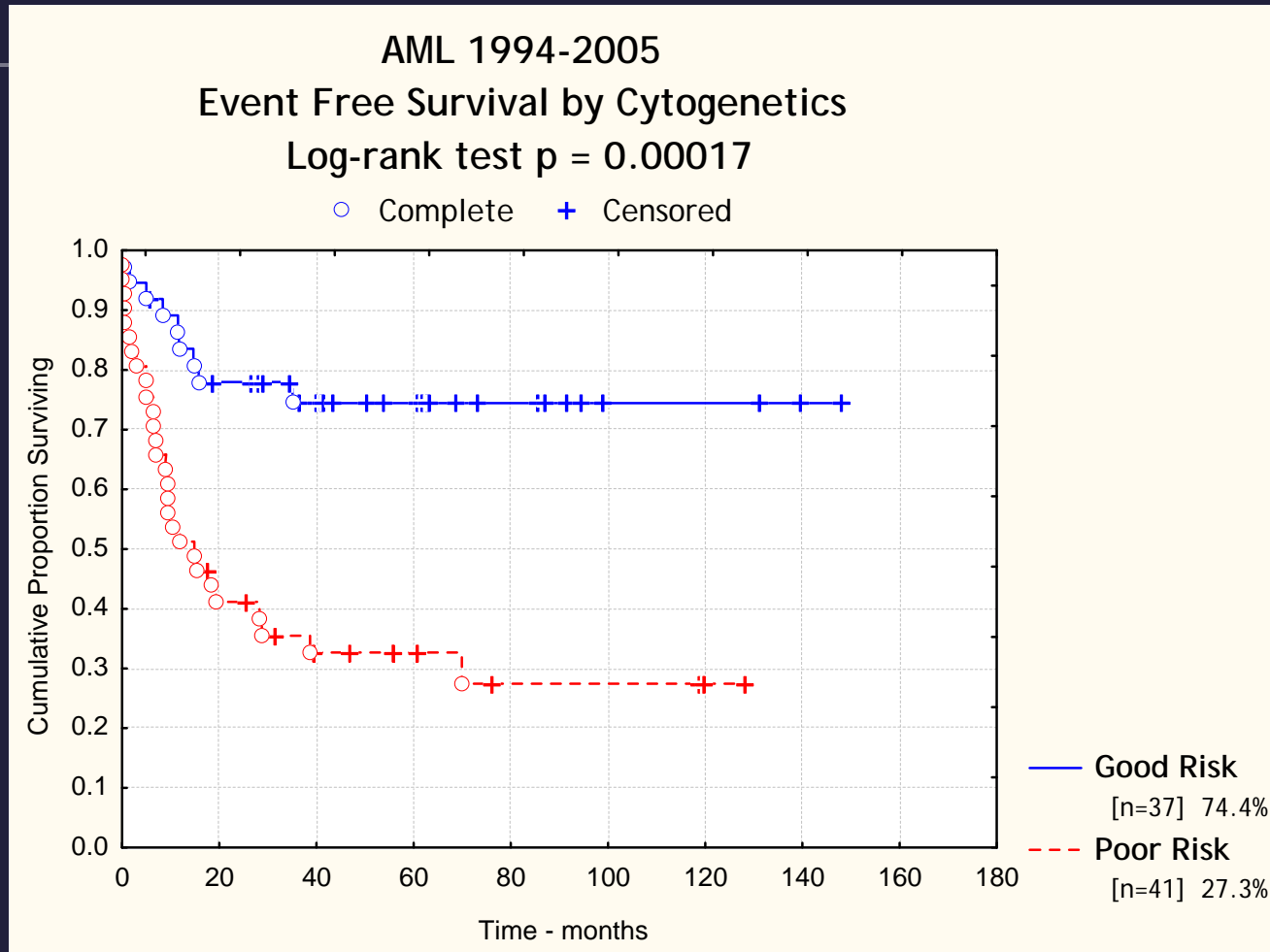
WHAT ABOUT RCCH?

- AML 1994-2005
- Chemotherapy was modified BFM-87
- Patients
 - Good risk (37) ... t(8;21) inv16 t(15;17)
 - Standard and Poor risk (41) ...
 - Normal / other cytogenetics 34
 - MLL gene 4 / MAKA 3
 - (Non-remitters 2)



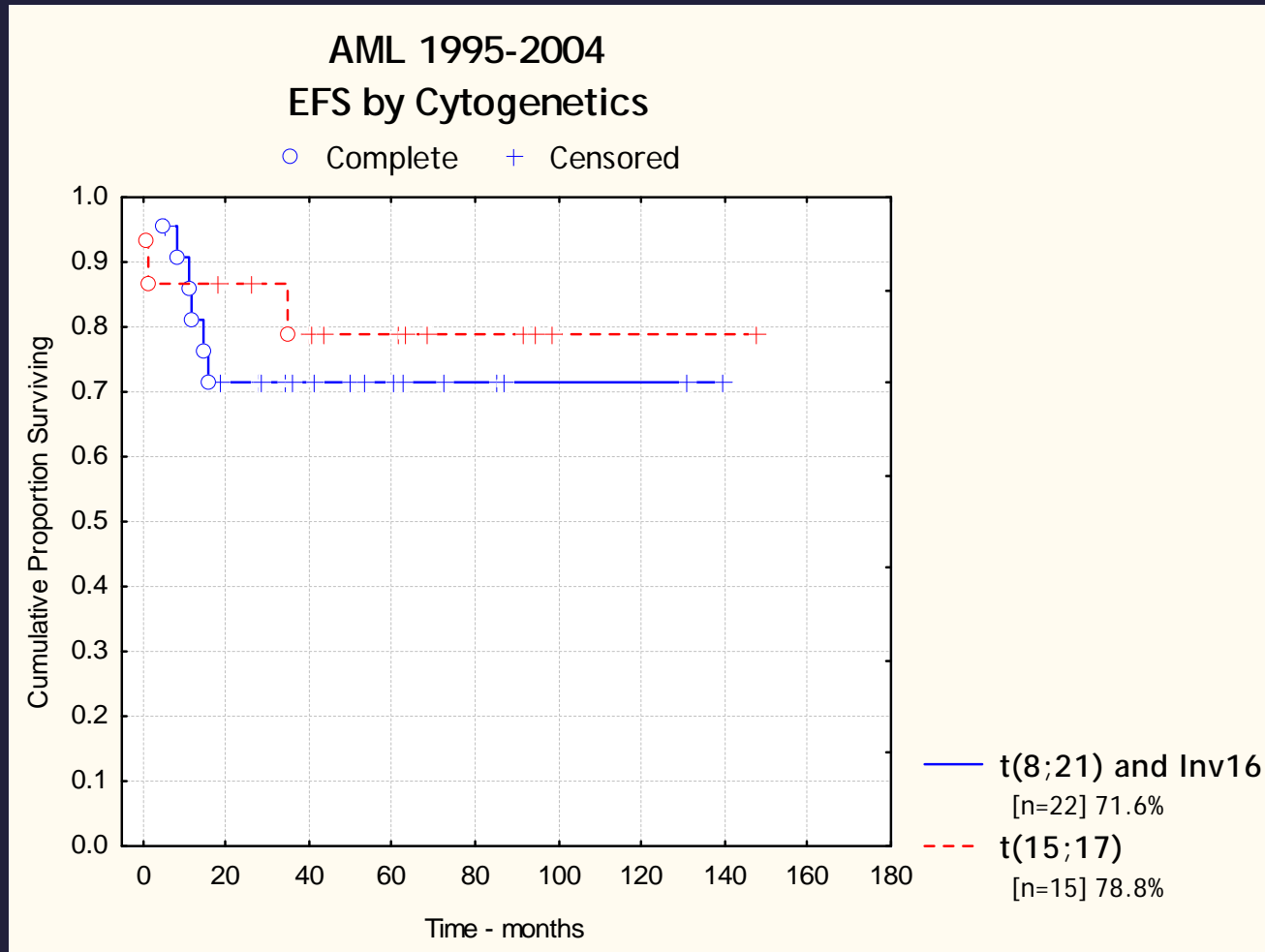
- Allo SCT for any standard or poor risk patient with a matched sib donor
 - 8 patients with matched sibs:
 - 3 good risk patients ADF in CR1
 - 2 SCT in CR1 – both ADF
 - 1 CBT in CR2 – DD
 - 2 were not transplanted - relapsed before SCT or did not achieve CR2

OUTCOMES for AML 1994-2005



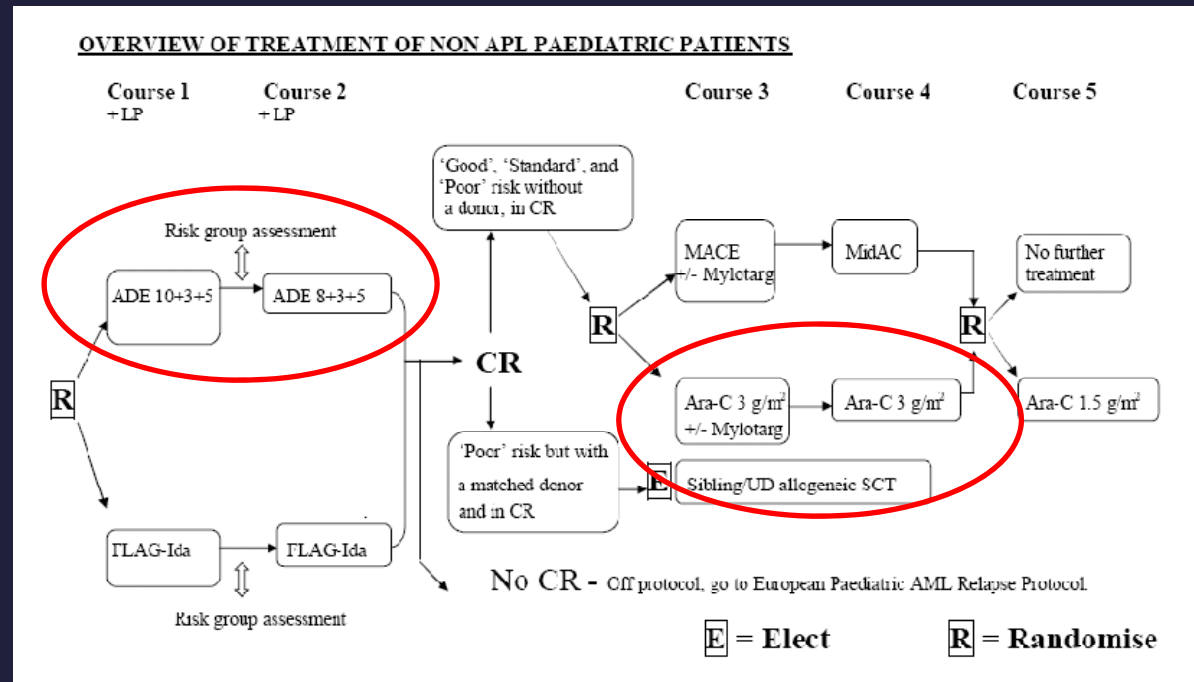
- Notably survival for M1,2 and 4 without favourable cytogenetics was 5/13 or 38%, making them at least standard if not poor risk.

OUTCOMES for AML 1994-2005



SO WHAT HAVE WE DONE?

- Outcomes for poor risk AML were poor
- Strategies to improve outcomes are:
 - More intensive chemotherapy: high dose AraC arm of MRC AML 15



- MUD SCT for selected cases in CR1 if we can find a local donor

NOW WHAT ABOUT THIS GUY?

- A 10 year old boy with M2 acute myelogenous leukaemia presents with a leukocyte count of $16 \times 10^9/L$
 - 30% myeloblasts (CD34+, DLA-DR+, CD33+, CD13+, CD7+)
 - normal male karyotype
 - 46 XY cytogenetics
 - CSF clear
- RISK ASSIGNMENT: STANDARD
- *As an aside ... CD7+ with normal cytogenetics suggests he may have CCAAT enhancer binding protein α (CEBPA) mutation but it's not specific and there's no data in paediatrics to consider it GOOD RISK!*

OPTIONS?

- MRC AML 15 high dose AraC arm (MUD SCT if necessary in CR2)
- MUD SCT in CR1

WE CHOOSE ...

- MRC AML 15 high dose AraC arm (MUD SCT if necessary in CR2)

- **MUD SCT in CR1**