

# MYELOABLATIVE CONDITIONING IN OLDER PATIENTS WITH HIGH RISK AML

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# The Challenge

- ◆ A 59-year-old man with adverse karyotype AML (monosomy 7) and no major co-morbidities, but bad osteoarthritis which keeps him in bed achieves CR after 2 induction courses – has an HLA identical sibling.
- ◆ He has done research on the internet and wants to know whether myeloablative or RIC will be used?

# What We Know

- ◆ Allogeneic Stem Cell Transplantation is most intensive post-remission therapy used for treating AML for more than 30 years.
- ◆ Relapse risk is considerably lower than with autologous transplantation or chemotherapy alone.
- ◆ High Treatment Related Mortality (TRM) continues to be a major limitation.

# Treatment Related Mortality

- ◆ Treatment related mortality is related to the direct toxicities of :
  - ◆ Conditioning Regimens
    - ◆ Interstitial Pneumonitis / Veno-Occlusive Disease
  - ◆ Graft vs Host Disease
    - ◆ Toxicity of conditioning can influence incidence and severity of GvHD.
- ◆ Despite long-standing use of AlloBMT – optimal myeloablative regimen unknown.

# CIBMTR Retrospective Review of MA vs RIC AlloBMT for AML

- ◆ Myeloablative SCT : 3 731 patients
- ◆ RIC SCT : 1 500 patients
- ◆ Median Age : MA – 42 years (16 – 68)  
RIC – 55 years (18 – 69)
- ◆ Median Follow-up : MA – 58 months  
RIC – 40 months

# 5-Year Probabilities of Outcomes after Different AlloSCT for AML

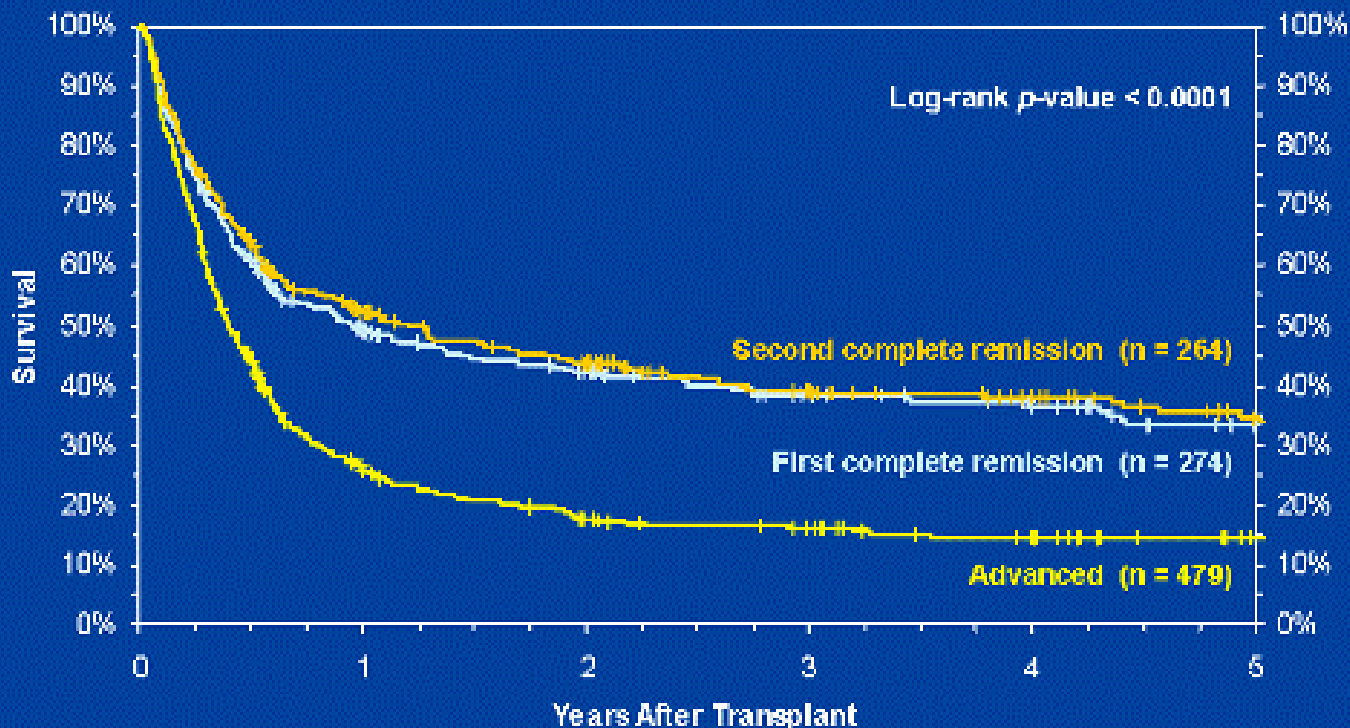
	<u>MA</u>	<u>RIC PBSC</u>	<u>RIC BM</u>	<u>NMA</u>
Relapse %	32	39	42	43
TRM %	34	34	37	36
LFS %	33	30	28	24
OS %	34	33	32	26

- ◆ MA regimens – significantly less relapse ( $p < 0.001$ ).
- ◆ Early TRM less with RIC/NMA regimens – 5 year TRM equivalent.
- ◆ Marginally better 5 year LFS ( $p = 0.05$ ) but similar OS ( $p = 0.25$ ) with MA vs RIC/NMA.

# When to Transplant

## Acute Myelogenous Leukemia

Survival of Adult (Age  $\geq 18$  Years) Marrow Recipients with Myeloablative Preparative Regimens, by Disease Stage 1998–2006

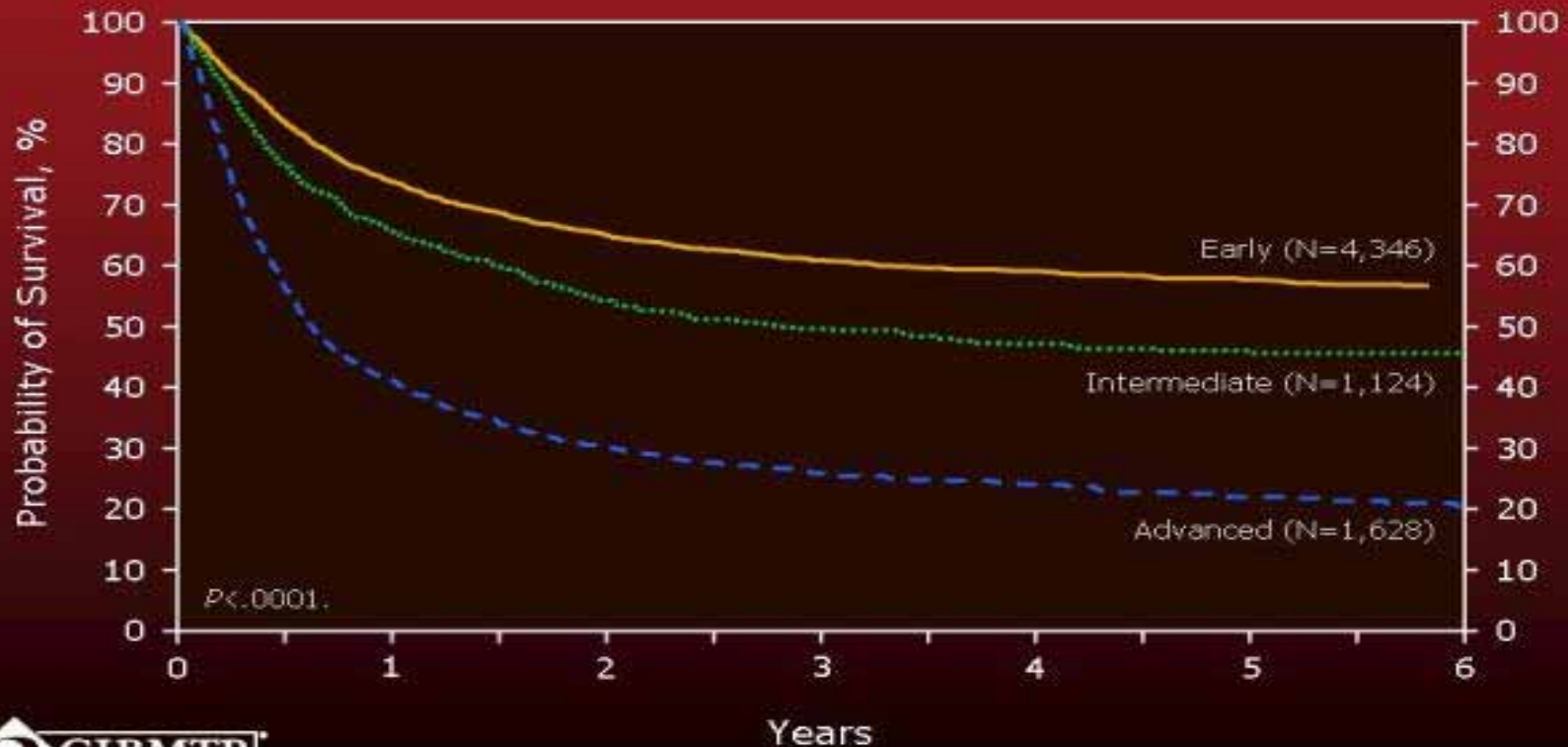


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# When to Transplant

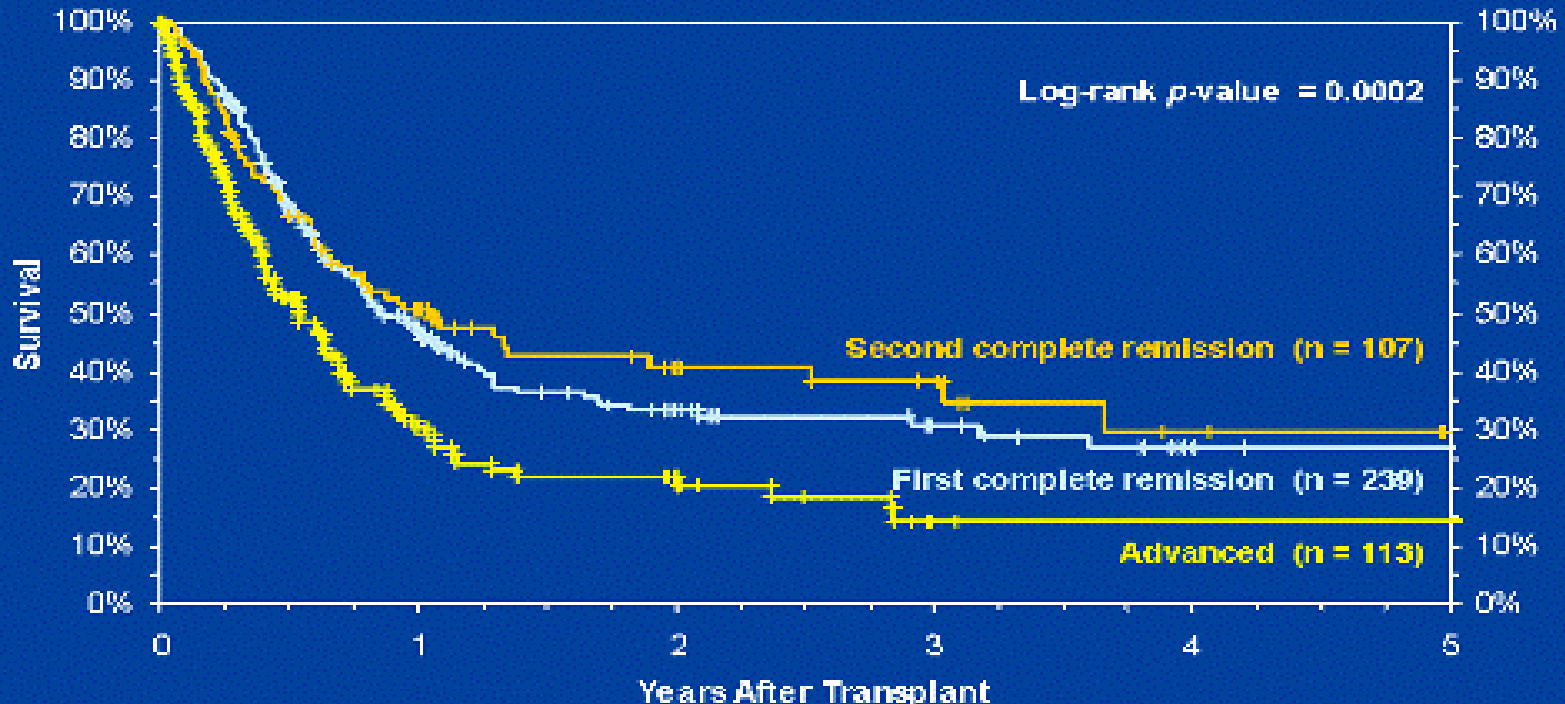
## Probability of Survival After HLA-Identical Sibling Transplants for AML With Myeloablative Conditioning, 1998–2006 By Disease Status



# When to Transplant

## Acute Myelogenous Leukemia

Survival of Older Adult (Age  $\geq 55$  Years) Marrow and PBSC Recipients with Non-Myeloablative Preparative Regimens, by Disease Stage 1998-2006



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# Cytogenetic Abnormalities

- ◆ Pretreatment cytogenetics has emerged as one of the most robust prognostic determinants of outcome in AML.
- ◆ Cytogenetics data is however not reported or unavailable in a large proportion of patients in studies comparing conditioning regimens.
- ◆ Several studies have used different definitions of “good risk” and “poor risk” AML – interpretation of this is difficult in the absence of well-designed randomized studies.

# Choice of Myeloablative Regimens

- ◆ The CyTBI and BuCy regimens have become the most widely used standard ablative regimens in AML.
  - ◆ Problems with determining superiority in AML CR<sub>1</sub>:
    - ◆ Limitation of randomized studies is the small number of subjects.
    - ◆ Observational database studies have large numbers (EBMT & IBMTR) – selection bias remains an issue for matching patient and disease characteristics.
  - ◆ Survival differences between the two regimens:
    - ◆ Multicentre French study only one to show superiority of CyTBI over BuCy in DFS (72 vs 47%) and OS (75 vs 51%).
    - ◆ Attributed to a lower relapse rate and lower TRM.
    - ◆ Other studies have failed to demonstrate survival benefits – mixed AML with other disease entities.

# Choice of Myeloablative Regimens

- ♦ Difference in Treatment Related Mortality:
  - ♦ No difference in incidence of acute or chronic GvHD have been observed between CyTBI or BuCy in registry database studies.
  - ♦ In randomized studies – more deaths from GvHD in BuCY group noted but in absence of pathological confirmation difficult to differentiate between VOD and GvHD.
  - ♦ Other complications appear to be more common in the BuCY group including VOD of liver / higher incidence of haemorrhagic cystitis / higher incidence of seizures.
- ♦ No differences demonstrated in engraftment rate between the two regimens.

# Myeloablation and Age

- ◆ Commonly 50 – 55 has been used as the upper limit for the use of myeloablative doses of chemotherapy due to perceived high rates of morbidity and mortality.
- ◆ Study presented at ASH 2008 from MD Anderson and University of Pisa to look at incidence of TRM.
- ◆ Study outline:
  - ◆ 74 patients over 55 years of age with either MDS / AML with poor cytogenetics in CR1 or multiply relapsed disease.
  - ◆ Regimen consisted of IV Fludarabine (40mg/m<sup>2</sup>) and IV Busulphan (130mg/m<sup>2</sup>) daily for 4 days.
  - ◆ GvHD prophylaxis consisted of Tacrolimus and Methotrexate.

# Myeloablation and Age

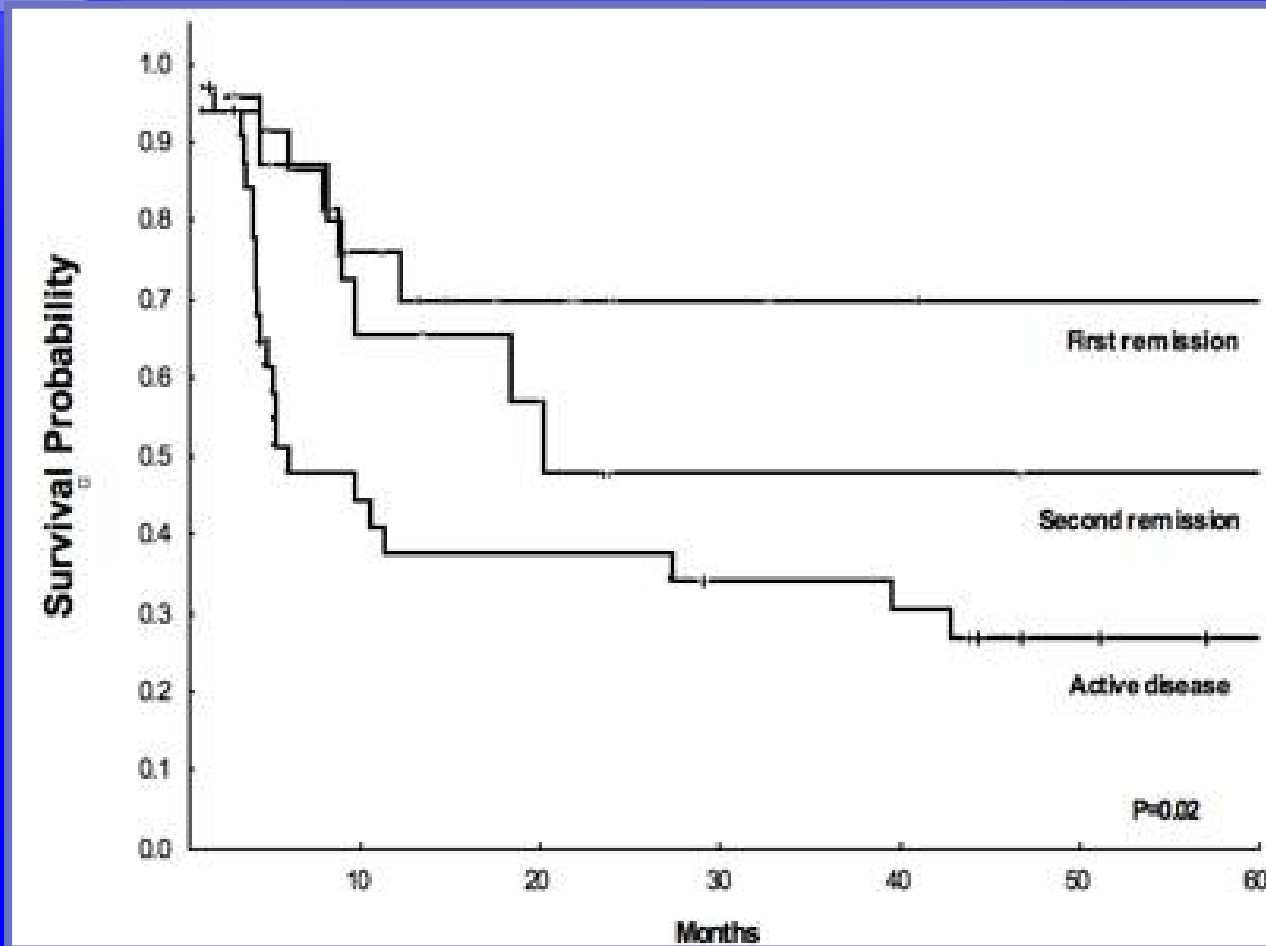
## ◆ Results of Study:

- ◆ Median age was 58 (55 – 66) – 24% over 60.
- ◆ 54% were in CR<sub>1</sub> at time of transplant.
- ◆ 68% and 28% had intermediate and poor risk cytogenetics respectively.
- ◆ All patients engrafted.
- ◆ 7% developed grade III or IV GvHD.
- ◆ Actuarial 2-year overall survival – 70%, 48% and 35% for patients in CR<sub>1</sub>, CR<sub>2</sub> or active disease at transplant.

# Myeloablation and Age

TRM	30 Days	100 Days	One Year
All Patients	None	4%	21%
All CR	None	5%	18%
CR 1	None	4%	15%
Persistent Disease	None	3%	27%

# Myeloablation and Age



# RIC / Non-Myeloablative Conditioning

- ◆ Main aim is to exploit beneficial graft-vs leukaemia effect and reduce regimen-related complications.
- ◆ Experience with AML is however LIMITED!
- ◆ High relapse rates continue to be a major issue.
- ◆ More disease-specific and long-term data needed to fully evaluate efficacy of these approaches.

# Conclusions

- ◆ Treatment related mortality remains largest concern with myeloablative conditioning regimens in AML:
  - ◆ TRM is not worse in patients undergoing MA SCT's.
  - ◆ Myeloablative regimens decrease relapse rates.
  - ◆ Age is NOT a contraindication to MA regimens.
  - ◆ No significant difference between different MA regimens – pros + cons of each need to be weighed up.

# Final Conclusion

“At present, myeloablative conditioning regimens, clinically tested for over 30 years, remain the gold standard of treatment and allotransplants with novel strategies for patients with high risk TRM should only be offered as a part of a clinical trial”.

## Mini Review

Myeloablative conditioning regimens for AML allografts: 30 years later. Gupta V, Lazarus HM, Keating A. Bone Marrow Transplantation (2003) 32, 969 – 978.