Timing of Autologous Stem Cell Transplant (auto-HCT) in MM: Early vs. Late? *In favor of late transplant*

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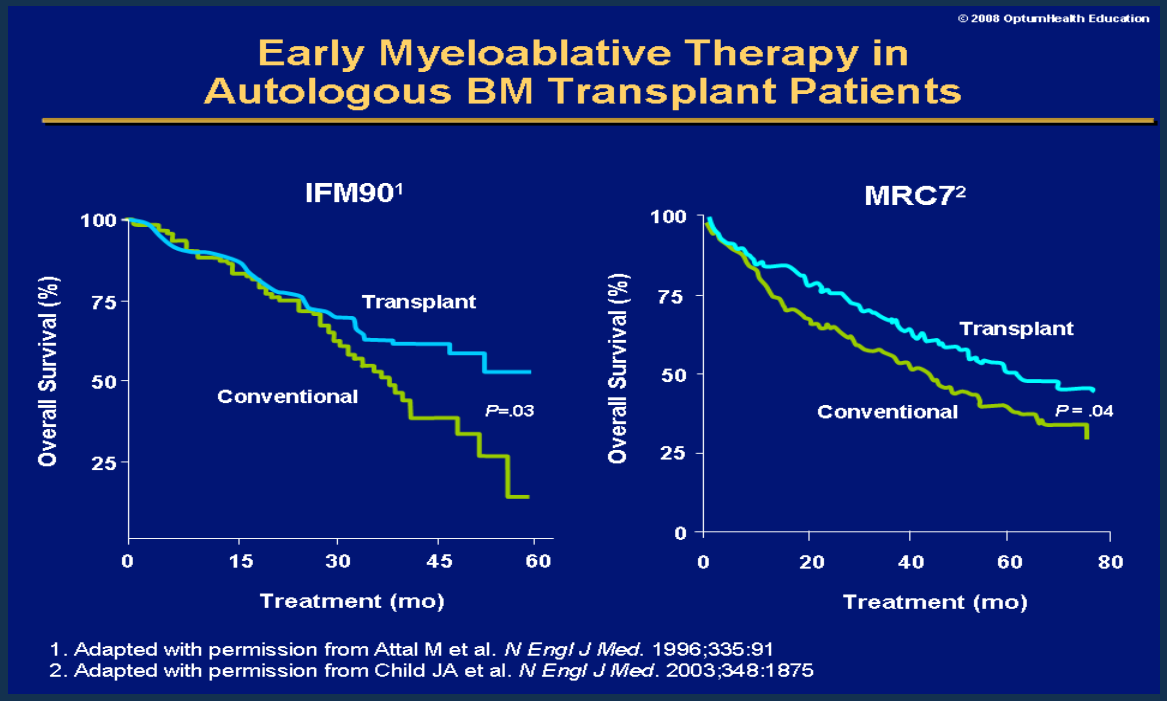
Auto-HCT Does Not Cure Myeloma

- Myeloma is perhaps the only malignancy in which auto-HCT is performed routinely without a curative intent



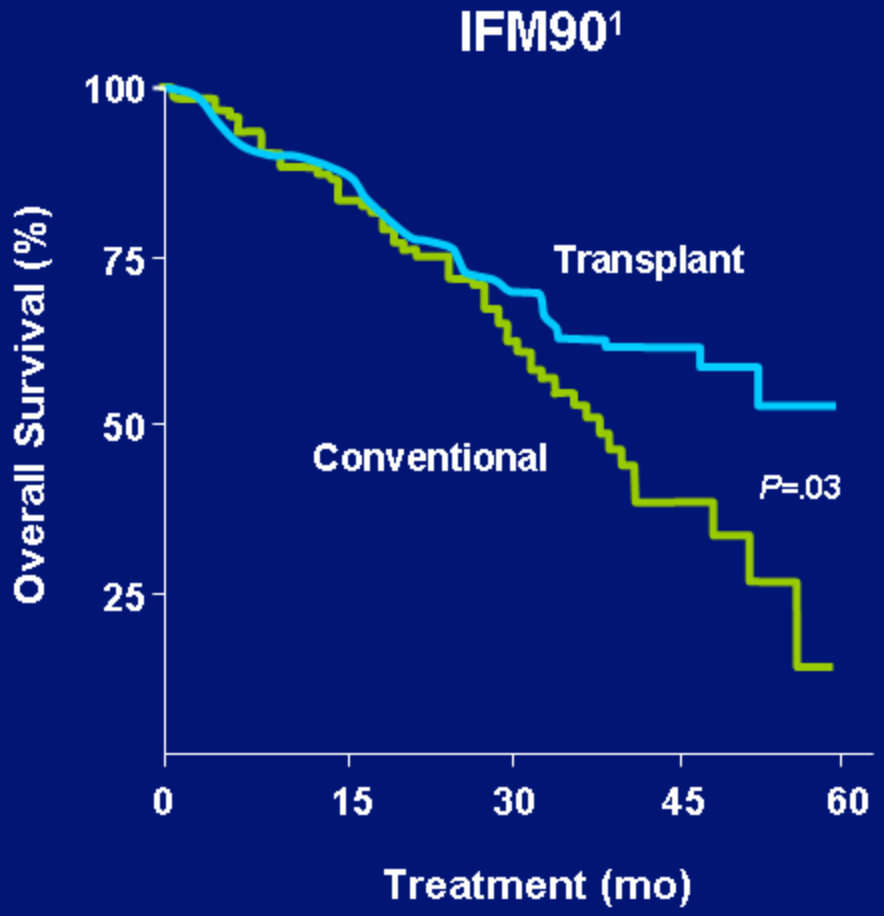
True Measures of Clinical Benefit

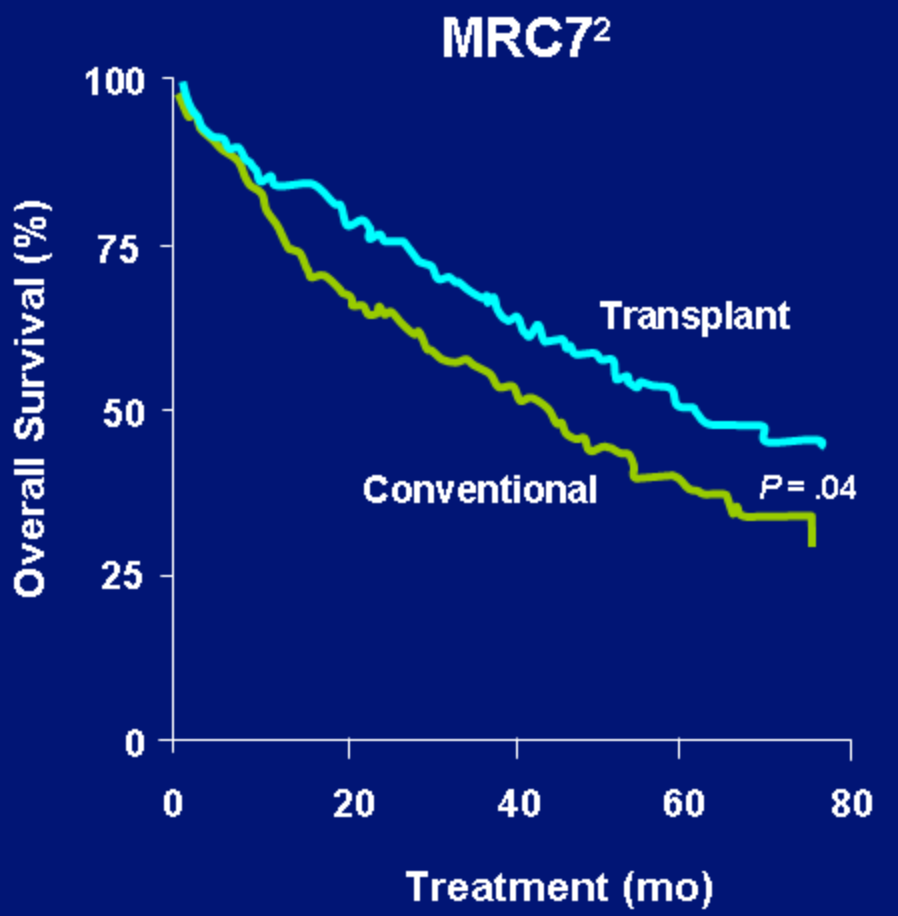
- Overall Survival
- Validated Quality of Life Outcome

Modest Clinical Benefit of early auto-HCT in "Positive" Studies

- Even in the 2 positive randomized trials of conventional chemotherapy vs. auto-HCT, the overall survival benefit was only 12-13 months
  - Attal M et al (NEJM 1996)
    - OS: 44 vs. 57 months
  - Child J et al. (NEJM 2003)
    - OS: 42 vs. 54 months

Early Myeloablative Therapy in Autologous BM Transplant Patients





1. Adapted with permission from Attal M et al. *N Engl J Med*. 1996;335:91
2. Adapted with permission from Child JA et al. *N Engl J Med*. 2003;348:1875

There were at least two "Negative" Randomized Trials

- Both the trials compared upfront auto-HCT vs. conventional chemotherapy, and both had about 200 patients
- Fermand JP et al. MAG 91. JCO 2005
  - Median EFS: 19 vs. 25 months (p=0.07)
  - Median OS: 47 vs. 47 months (p=0.91)
- Blade et al. PETHEMA. Blood 2005
  - Median EFS: 33 vs. 42 months (p=0.57)
  - Median OS: 66 vs. 61 months (p=0.89)

Two Randomized Trials Compared Early Vs. Delayed Auto-HCT

- The real evidence against early auto-HCT are these two randomized trials
  - Fermand et al. MAG 91 Trial.
  - Barlogie et al. US Intergroup Trial
- They did NOT show any improvement in OS with upfront transplant

blood
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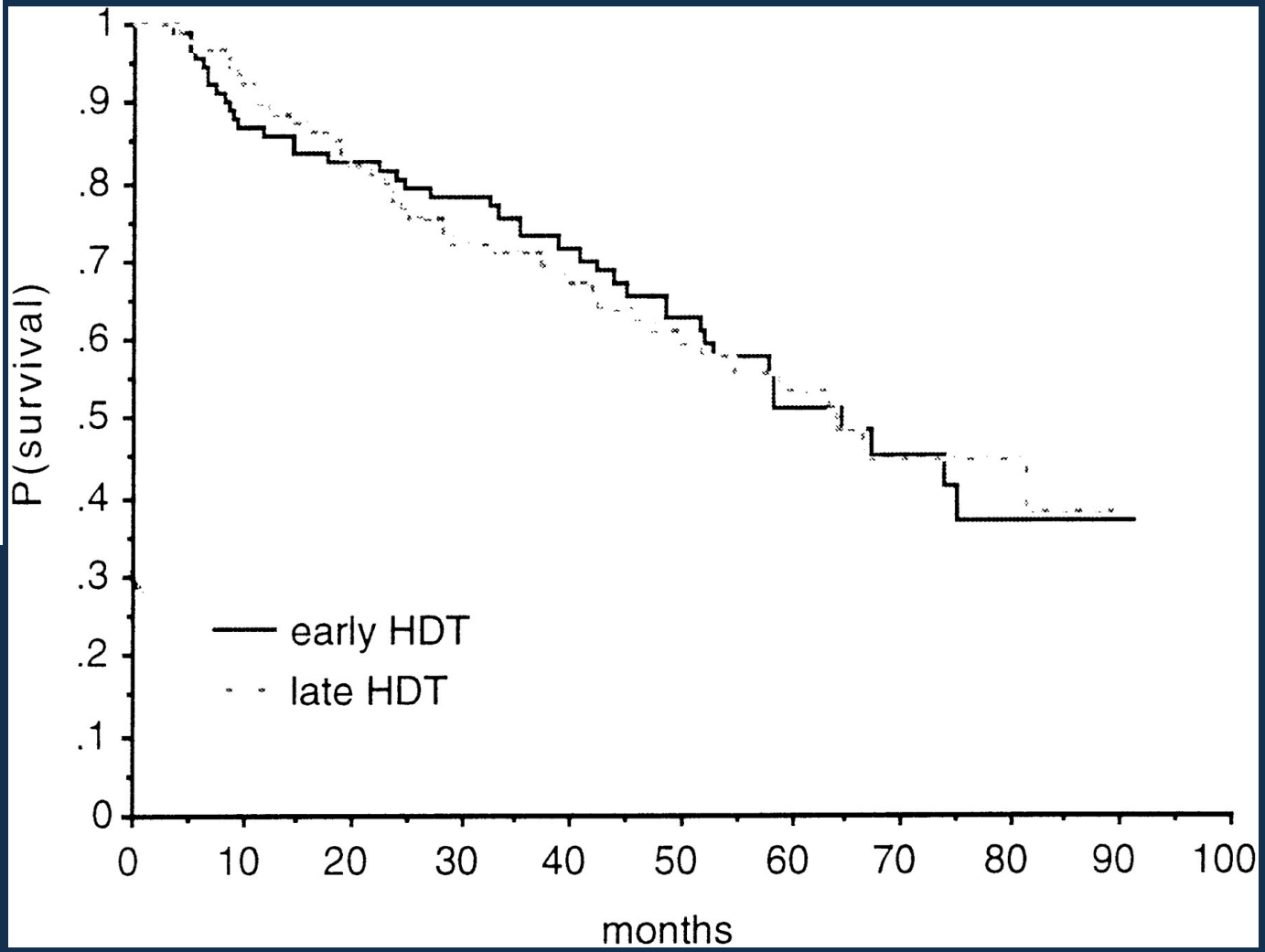
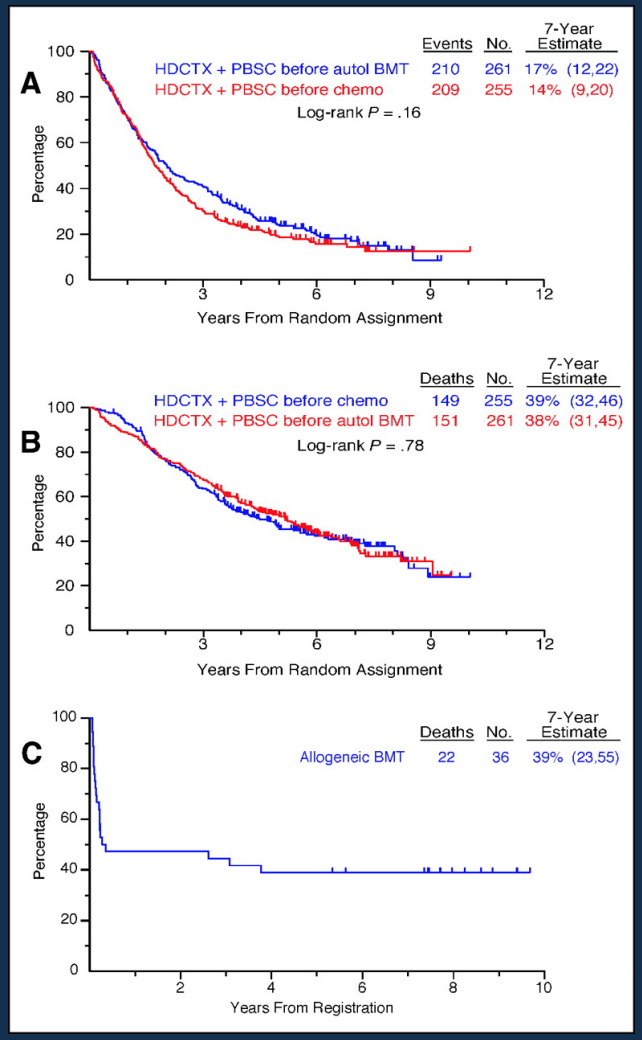
OS according to treatment group.



Fermand J et al. Blood 1998;92:3131-3136

(A) Progression-free survival (PFS) and (B) overall survival (OS) from first randomization assignment.



Barlogie B et al. JCO 2006;24:929-936

Depth of Response with Novel Agents Equally Good

- The real benefit from auto-HCT was from the depth of response; with newer agents the depth of response is comparable without transplant
  - Cavo M. VTD vs. VD. Lancet 2010
    - Post induction CR: 31%
  - Jakubowiak A. CRD
    - sCR: 61% without auto-HCT

No More Long Treatment-Free Interval

- Previously, auto-HCT used to be followed by observation only, an attractive option for many patients
- Now almost all the patients are encouraged to receive consolidation and maintenance therapy
  - Cost
  - Adverse events
  - QOL

Risk of Second Primary Malignancies (SPM)

- Maintenance therapy is increasingly used with the recent results of lenalidomide maintenance trials
- The incidence of SPM is universally higher with lenalidomide maintenance (up to 8%)
- That may put many patients at an even greater risk who may not have needed the auto-HCT in the first place

Just Another Treatment Option

- Auto-HCT is just another treatment option and should be individualized
- Delayed transplant may allow patients to go through years of Rx without suffering the toxicities of high dose alkylators and without facing 2-3 months of disruption of daily life that comes with transplant
- With this approach, 50% of patients are opting for a deferred transplant
- Delaying transplant makes economic sense also, since half the patients don't get the Rx, with the same survival

Proposals

- Patients should make the choice after unbiased information is provided about the modest benefit of auto-HCT
- Patients should be treated on clinical trials of early vs. delayed transplant using current anti-myeloma agents
- Endpoints should be OS and/or QOL, and not surrogates like CR or PFS