DO WE STILL NEED AUTOTRANSPLANTS FOR MYELOMA IN THE ERA OF NOVEL THERAPEUTICS?

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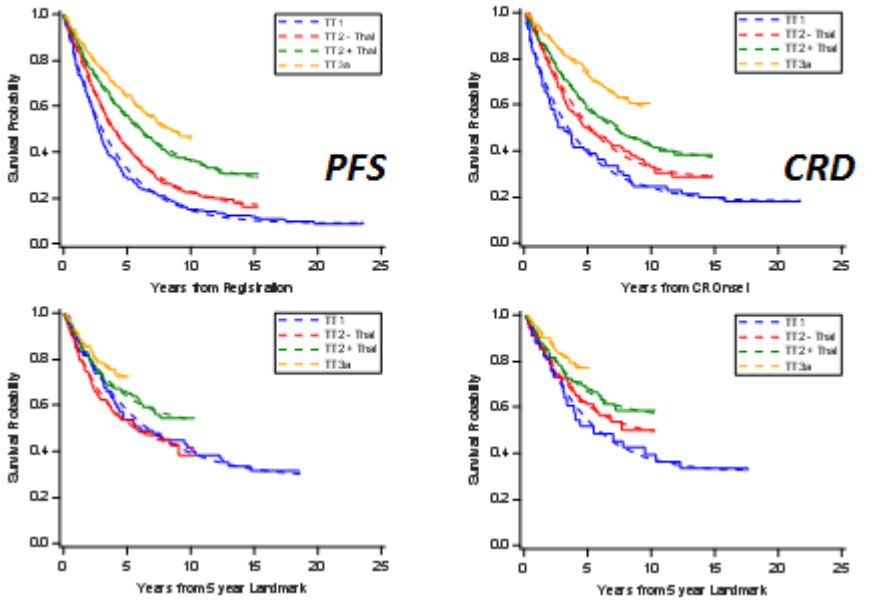
In the era of novel agent combinations, high CR rates of up to 60% have been reported so that the role of auto-transplants (AT) in the upfront management of multiple myeloma (MM) has been questioned. Several randomized trials have addressed this issue. Cavo et al reported on the EMN02/HO95 trial that employed VCD x 4 for induction with a first randomization R1 to 1 or 2 AT versus VMP for 4 cycles and further randomization R2 to consolidation or not with VRD x 2 cycles, followed by lenalidomide maintenance. PFS was superior with AT ($p=0.003$), pertaining to both low and high risk cytogenetics. AT randomization was an independent favorable variable with HR=0.54 ($p<0.001$). Follow up was too short to comment on OS. The GIMEMA trial reported significantly superior PFS and OS with 2 AT compared to MPR x 6 as did another MultiCenter trial comparing 2 AT with CRD x 6. IFM2009 reported superior PFS in the AT group ($p<0.001$), also when considered on multivariate analysis ($p=0.02$). MRD occurred in 79% on AT versus 65% on VRD arm ($p<0.01$). As MRD predicted for superior OS ($p<0.001$), OS is expected to be superior with AT.Jakubowiak et al explored AT after 4 cycles of KRd induction, followed by 4 further cycles of KRd consolidation and KRd maintenance. Compared to an earlier phase I/II study with KRd without AT (n=53), AT added to KRd (n=62) raised sCR rate to 87% from 55% after 18 cycles of KRd; the 2-year PFS was 98% versus 92% without AT. With the recent introduction of daratumumab, elotuzumab and nivolumab, further progress is anticipated. Targeted therapies have also proven to be effective (trametinib for RAS-mutated MM). We have recently reported on the curability of MM with Total Therapy (TT) (Blood 2014), noting the importance of long term follow up of 10+ years in order to discern the emergence of cure plateaus. Cure fraction (CF) estimates based on CR duration (CRD) curves revealed a steady increase from 18% with TT1 to 28% with TT2 control arm to 36% with TT2 + thalidomide to 49% with TT3 incorporating bortezomib. Multivariate analysis of pre-treatment variables revealed the dominance of gene expression profiling (GEP) defined high risk (15%) for CRD with a hazard ratio of 8.2 ($p<0.0001$) accounting for 40% on R2 analysis.As the 15% of patients with GEP defined high risk MM have not benefited from successive TT trials with median PFS and OS of 2 to 3 years, we are exploring AT-free therapy with 28-day metronomically scheduled VTD-ADR-DDP, inducing high CR rates of nearly 80% after a single cycle followed by nivolumab or daratumumab maintenance.

	TT1	TT2 (- / + thal)	TT3
Induction	VAD X 3	VAD	VTDPACE - HPC
	CTX – HPC	DCEP	VTDPACE
	EDAP	CAD – HPC	
		DCEP	
Transplant	MEL200	MEL200	MEL200
	MEL200	MEL200	MEL200
Consolidation	----	DPACE X 4	VTDPACE X 2
Maintenance	IFN	IFN + DEX	VTD

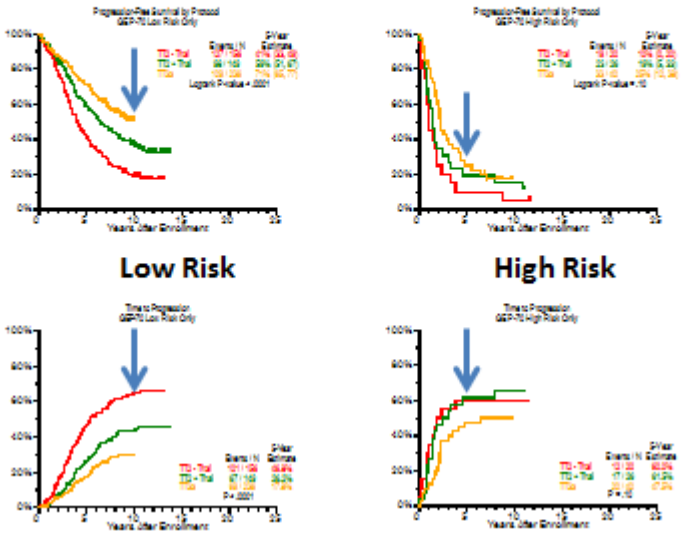
Cure Model Estimates from Baseline and from 5 Year Landmark

Cure model estimates are shown by the dotted lines. Kaplan-Meier estimates are shown as solid lines.



Progression Estimates by Protocol and GEP-70 Risk

Common to all endpoints examined, plateaus are reached earlier at 5yr in high-risk compared to 10yr in the majority of 85% with low-risk myeloma



Low Risk **High Risk**