CURING MYELOMA: FOCUS ON HIGH RISK DISEASE CRUCIAL TOWARD FURTHER PROGRESS

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Most presentations on MM begin with “MM is an incurable malignancy”. Access to well annotated long term follow up data of patients enrolled in Total Therapy (TT) protocols, TT1 (n=231), TT2 (n=668) and TT3a (n=303) with median follow-up times of 21yr, 12yr, and 9yr, has enabled us to define criteria for curability in MM (Blood 2014). TT backbones consisted of induction therapy with HPC collection, tandem transplants with melphalan 200mg/m2, consolidation introduced in TT2, and maintenance. TT2 randomized patients between a control arm and thalidomide from treatment inception through maintenance, while TT3a incorporated bortezomib into induction, consolidation and maintenance phases together with thalidomide. A modified Weibull statistic was applied and cure-compatible plateaus observed for both CR duration (CRD) and progression-free survival (PFS) without CR, implying durable MM control with MGUS-like background. PFS/CRD estimates increased from 9%/18% in TT1 to 16%/28% in TT2 without thal (TT2-) to 25%/36% in TT2+thal to 33%/49% in TT3a. When measured from a 5-yr landmark, the corresponding numbers were 28%/32% with TT1, 39%/47% with TT2-, 51%/56% with TT2+, and 70%/75% with TT3a. Gene expression profiling (GEP) of purified plasma cells became available half-way though accrual to TT2. Examination of PFS and time to progression (TTP) according to GEP-70 risk revealed significant improvements in the 85% with low-risk MM so that 5-yr PFS increased from 41% with TT2- to 59% with TT2+ to 71% with TT3a ($p<0.0001$), which was accompanied by significant reduction in 5-yr TTP from 47% with TT2- to 26% with TT2+ to 18% with TT3a. Among the 15% of patients with GEP-70 high-risk MM, only minor improvements were appreciated with 5-yr PFS of 10% with TT2-, 19% with TT2+, and 25% with TT3a ($p=0.10$); TTP was reduced from 61% with both TT- and TT2+ to 48% with TT3a ($p=0.10$). Importantly, plateaus were reached earlier in high-risk MM at ~ 5yr as opposed to ~10yr in the case of low-risk MM. We conclude: (1) Applying all active treatment principles upfront, MM cures have been documented with increasing frequency as a result of adding novel agents into the TT tandem transplant backbone. (2) Sustained PFS without CR reflects re-establishment of a MGUS-like state. (3) Cure rates in low-risk MM reach 50% when bortezomib was added in TT3a, and a 15% cure rate pertains to high-risk MM observed earlier at 5yr rather than 10+yr in low-risk MM. (4) Novel concepts should be tested in GEP-defined high-risk MM with a median PFS not exceeding 2yr so that valuable information should be available within 3yr of follow up. (5) In low-risk MM, >10yr follow up is needed for curability with only novel agents without transplants to be determined. Earlier surrogate markers such as flow cytometry based MRD, MRI-CR and GEP-based normalization of whole bone marrow biopsies are under investigation.