University of Arkansas for Medical Sciences

Impact of Total Therapies on clinical outcome of myeloma stratified by risk and molecular subgroups

Christoph J. Heuck[1], Niels Weinhold[1], Sharmilan Thanendrarajan[1], Caleb K. Stein[1], Frits Van Rhee[1], Adam Rosenthal[2], Yogesh Jethava[1], Rashid Khan[1], Antje Hoering[2], Faith E. Davies[1], Bart Barlogie[1] and Gareth J. Morgan[1]

[1]Myeloma Institute, UAMS, Little Rock, AR; [2]Cancer Research And Biostatistics, Seattle, WA;

Background

Despite the introduction of new agents multiple myeloma (MM) is a disease with unpredictable clinical course consistent with it being composed of a variety of subtypes with distinct molecular features. In order to shed light on the impact of this molecular heterogeneity on treatment response we examined clinical outcomes in our series of Total Therapy (TT) trials, stratified by risk status and molecular subgroup.

Methods

The TT trial program at UAMS, comprising TT1-5, included a total of 1,808 patients enrolled on or prior to October 28, 2014. An overview of the trials is provided in Supplementary Figure 1. Baseline gene expression profiling (GEP) data was available for 1,217 of these patients. Informed consent for treatment and sample procurement was obtained for all cases included in this study, in accordance with the Declaration of Helsinki. An overview of the treatments for TT1-5 protocols is shown in **Table 1**.

Gene expression profiling was performed with the Affymetrix U133Plus2.0 microarray platform (Santa Clara, CA) using methods previously described. All data used in these analyses were derived with the Affymetrix Microarray GCOS1.1 software.

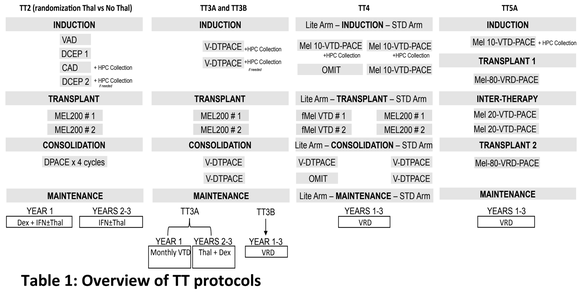

Table 1: Overview of TT protocols

Results

The HY group was the largest subgroup (n=380, 31%), followed by CD-2 (n=186, 15%), MS (n=170, 14%), LB (n=166, 14%), PR (n=158, 13%), CD-1 (n=85, 7%) and MF (n=72, 6%). The distribution of the molecular subgroups in each TT trial is shown **Figure 1A**.

Results (continued)

80% high risk (HR) cases were assigned to the subgroups MS, MF, and PR. Amplification of 1q21 (by iFISH) was see in at least 60% of MS, MF and PR cases (**Figure 1B**).

Interestingly gain of 1q21 was frequently detectable in LB cases, a subgroup with a generally a very good outcome. The overwhelming majority of cases in CD-2, HY and LB are classified as LoR (**Figure 1C**). cases classified as LoR (risk score<0.66), the molecular subgroups MS, MF and PR have elevated risk scores in comparison to the remaining groups (**Figure 1D**)

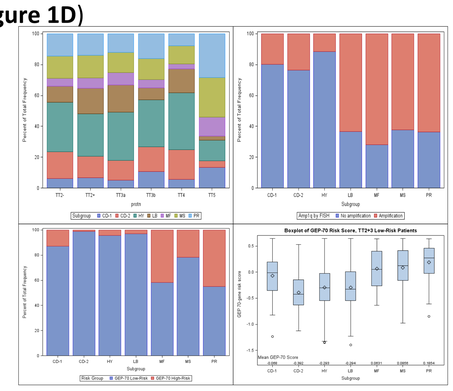

Figure 1: Distribution of molecular features across different TT protocols and molecular subtypes. A) Distribution of molecular subtypes within different protocols B) prevalence of amplification of chromosome 1q21 across different molecular subgroups C) distribution of GEP70 defined risk across different subgroups D) distribution of GEP70 risk scores for GEP70define low risk disease only across different molecular subgroups.

Results of the comparison of TT2- to TT2+ suggest that the addition of thalidomide positively affected the PFS of HY (HR=0.62, *P*=0.034), LB (HR=0.44, *P*=0.018) and MS (HR=0.42, *P*=0.005) (**Figure 2**). In TT3A, bortezomib was introduced into the induction, consolidation and maintenance phase of therapy in addition to thalidomide further improving PFS of the MS in comparison to TT2A (HR=0.52, *P*=0.048). The OS of the MS subgroup became comparable to the CD-1, CD-2, HY and LB subgroups, which were associated with an estimated 5-year OS of at least 77% (**Figure 3**). The MF and PR groups showed no significant improvement and they remained the groups with the worst outcome in MM with a 5-year PFS estimate of 46% each and OS of 46% and 55%, respectively (**Figure 3**).

Results (continued)

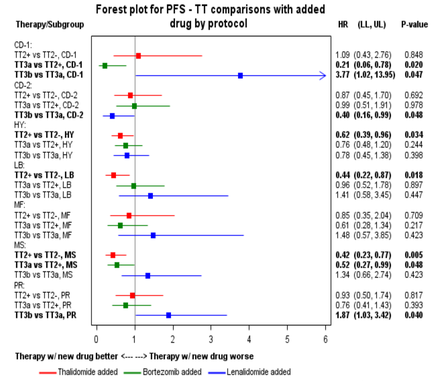

Figure 2: Impact of novel therapies on hazard ratio for different molecular subgroups in different TT trials.

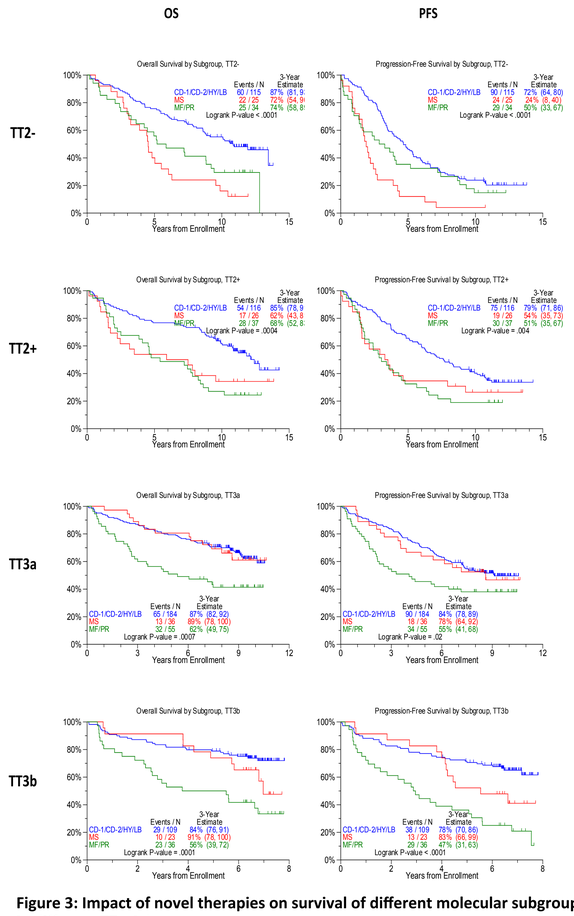

Figure 3: Impact of novel therapies on survival of different molecular subgroups in different TT trials.

Results (continued)

We performed a landmark analysis from the start of maintenance to check whether maintenance with novel drugs improved survival of risk groups. The results indicate that the use of thalidomide and bortezomib during maintenance of TT2+ and TT3a respectively positively impacted the PFS and OS of LoR cases Selection bias has to be discussed.

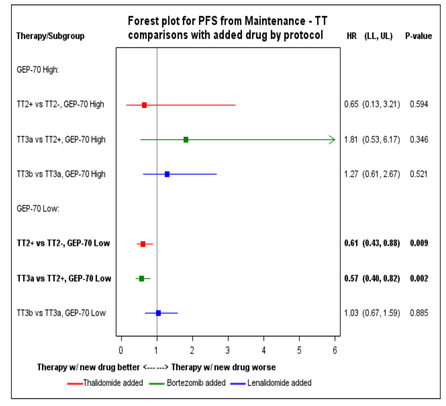

Figure 4:: Impact of novel therapies on maintenance

CR rates in high-risk (HR) MM are similar to LRMM. Yet a more dose-dense chemotherapy in Total Therapy (TT) 5 failed to improve survival in HRMM. For HRMM treated on TT2 and 3, treatment failures occurred early in the inter-transplant or consolidation phases. Interestingly with dose dense therapy in TT5 treatment failure was not seen until the maintenance phase.

Conclusion

HRMM has a distinct clinical course with high rates of primary refractory disease and early relapse. Changing therapy for HRMM from dose intense to dose dense has shifted treatment failure from the inter-transplant to the maintenance phase, which is now a setting where novel approaches can be used. For LRMM we can define distinct clinical response and outcome patterns dependent upon GEP-defined molecular subgroups. This differential response dependent upon treatment used at induction opens the potential for adjusting maintenance to take account of the disease subtype.