Curing myeloma at last - Defining criteria and providing the evidence

Running head: Curing myeloma

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Abstract

We examine whether the historical dogma of multiple myeloma being incurable still holds true. The genomic chaos and resulting resistance to apoptosis of myeloma, long considered an obstacle to cure, formed the basis of the Arkansas Total Therapy (TT) program. The TT approach employs all myeloma-active drugs up-front to target drug-resistant sub-clones during initial treatment to prevent later relapse. Long-term follow up of altogether 1202 patients enrolled (TT1: n=231, median follow up: 21yr; TT2: 668, median follow up: 12yr; TT3a: n=303, median follow up: 9yr) permitted investigation of whether progression-free survival (PFS) and complete response (CR) duration were consistent with curability, i.e. observation of plateaus in Kaplan-Meier plots for PFS and CR duration. In the subset of 627 patients with plasma cell gene expression profiling data, cure plateaus were apparent at 5 years in the 14% with high-risk myeloma compared to 10 years in the remainder with low-risk disease. A parametric model based on PFS and CR duration supported an increase in curability with successive trials. Thus, 10-yr PFS and CR estimates increased from 8.8%/17.9% in TT1 to 15.5%/28.2% in TT2’s control arm to 25.1%/35.6% in TT2’s thalidomide arm and to 32.9/48.8% in TT3a. Toward developing novel therapies, we recommend a concerted focus on patients with high-risk myeloma whose outcome has not been advanced.
Introduction

Multiple myeloma (MM) is widely considered incurable, although some investigators have recently challenged this dogma (1, 2, 3, 4, 5, 6, 7, 8). A minimum of 10 years seemed to be required to determine whether a plateau in progression-free survival (PFS) has emerged. The median follow-up times of initial trial reports are in the 3 to 5 year range. Subsequent reporting of mature data is sparse preventing determination of curability. Here we address the curability of myeloma from the vantage point of having followed all patients treated in the Arkansas program for life.

The presence of profound intra-tumoral heterogeneity (ITH) is thought to be the root cause for the perceived lack of curability in MM (9, 10). ITH increases progressively from the stages of monoclonal gammopathy of undetermined significance (MGUS) (11) and asymptomatic MM (AMM) (12) to symptomatic or clinical MM (CMM) requiring therapy (13). Such genomic chaos formed the rationale for applying all MM-active therapies up-front in our Total Therapy (TT) trials aimed at eradicating preemptively drug-resistant MM sub-clones. Incorporating new agents with novel mechanisms of action into transplant trials has markedly contributed to improved outcomes (14) by achieving high rates of complete remission (CR) as an essential first step toward long-term disease control and cure (15, 16, 17). Recent trials with novel agent combinations have achieved high CR rates comparable to those previously reported only with transplants (18). The quality of comparable rates of CR effectuated by different treatment approaches can be judged by their durability after cessation of treatment. It is hoped that more refined measurements of the depth of response can provide valuable early surrogates for the anticipated duration of MM control. The detection of minimal residual disease (MRD) by flow cytometry (19, 20) and the use of other biomarkers of cure are important for the early assessment of long term outcome and consequently more rapid progress toward curative therapies.

Intra-tumor heterogeneity is a hindrance to cure

One of the major impediments to curing MM is ITH. This term refers to the co-existence of tumor sub-clones displaying differences in drug sensitivity, explaining the
Darwinian basis for myeloma progression and the development of drug resistance (21). We described the presence of ITH using next generation sequencing and single cell analyses (22, 23). Based on results of whole-genome sequencing of samples from MGUS, high-risk AMM and CMM, it has been demonstrated that most genetic changes in CMM are already present at the AMM stage and concluded that clonal progression is the key feature of transformation from benign clinical disease to CMM (24). The clinical importance of ITH is also illustrated by the use of genome mapping technology (25). In response to various two- or three-drug combinations, a “clonal tiding” pattern was observed (26), where different and progressively fewer dominant clones emerged during serial relapses.

Direct clinical evidence for ITH comes from modern imaging studies. We showed persistence of MRI-defined focal lesions in serological and hematological CR (27), extending to the level of minimal residual disease (MRD) negativity defined by multicolor flow cytometry (28). With further follow-up, about 60% of patients qualified for MRI-defined CR (MRI-CR) emerging almost 2 years after onset of clinical CR. PET scan findings of baseline differences in metabolic activity of intra-medullary focal lesions regressing after therapy with different kinetics underscore to the clinical observer the reality of ITH (29, 30, 31).

**Update on Total Therapy trials provide evidence of curability in MM**

Based on the presence of clonal heterogeneity (32, 33), we applied the St. Jude Total Therapy concept of employing all active treatment ingredients, which has been highly successful in pediatric ALL (34), to presenting newly diagnosed cases with CMM. The primary components of our successive trials are given in Figure 1. TT1 results proved to be superior to outcomes reported from a contemporary US cooperative group trial (35). Thalidomide’s remarkable activity in relapsed refractory MM (36) formed the basis for initiating TT2 as a randomized phase III trial with thalidomide in the experimental arm (37). Compared to TT1, TT2 induction therapy also included a series of non-cross-resistant combinations prior to and introducing consolidation chemotherapy following melphalan-based tandem transplants, which was followed by dexamethasone plus interferon as indefinite maintenance. The activity of bortezomib in
advanced and refractory MM (38) provided the basis for adding this proteasome inhibitor up-front in TT3a (39, 40, 41, 42). The basic schema of induction, tandem transplant and consolidation remained as in TT2. All patients received thalidomide based on the superior results obtained in the thalidomide arm (43). Maintenance consisted of 1 year of bortezomib and 2 years of dexamethasone plus thalidomide.

The baseline characteristics of patients accrued to TT trials are similar across studies (Supplemental Table 1). Clinical outcomes, updated March 26, 2014, are presented in Figures 2 and 3. The median follow-up is 21 years for TT1 (n=35/231), 12 years for TT2 (n=258/668), and 9 years for TT3a (n=187/303). OS and PFS plots progressively move closer together with each successive TT trial so that the ratios of estimated 5-year OS-to-PFS decrease (TT1, 2.1; TT2-Thal, 1.6; TT2+Thal, 1.2; TT3a, 1.1) (P<0.001) (Figure 2A-D). Thus, while increased use of all available therapeutic tools upfront shortened post-relapse survival, the gap between OS and PFS narrowed toward increasing cure fractions. With the transition from TT1 to later trials, significant improvements occurred in patient OS and PFS (Figure 2E-F). We next examined response and progression estimates which all were favored with transition to later protocols (Figure 3). Importantly, despite similar cumulative incidence of CR plots, CR duration (CRD) in TT3a, incorporating upfront bortezomib, was significantly prolonged in comparison with TT2+Thal (Figure 3A-B). This observation suggests that TT3a promoted a deeper level of CR, which we hope to quantitate by MRD flow cytometry in current trials. The 5-year estimates of time to progression (TTP) and time to relapse (TTR) from CR progressively declined in successive trials: 59% and 58% in TT1, 43% and 41% in TT2–Thal, 28% and 33% in TT2+Thal, and 22% and 18% in TT3a, respectively (Figure 3C-D).

A subset of 627 patients enrolled in TT2 and TT3a trials had available GEP data. Outcomes differed markedly between GEP70-defined low-risk and high-risk disease (Figure 4): 5-yr PFS rates for low-risk CMM were 41% in TT2–Thal, 59% in TT2+Thal, and 71% in TT3a (p<0.0001) (Figure 4A), while those for high-risk CMM were 10%, 19%, and 25%, respectively (p=0.10) (Figure 4B). Estimates of TTP showed significant declines with later protocols only in low-risk and not in the high-risk subgroup (Figure 4C-D). While the cumulative incidence of CR within a given protocol did not differ
between the 2 risk groups (Figure 5A-B), gains were apparent for CRD in low-risk but not in high-risk disease (Figure 5C-D). Interestingly, PFS, CRD and TTP curves reached plateaus at approximately 5 years in high-risk CMM, as opposed to more than 10 years in low-risk CMM.

Several statistical models were used to analyze TT outcomes. Relative survival was calculated as the ratio of observed to expected survival, based on US population life tables matched for age and gender (44); the ratios were estimated at 1-year intervals, given survival to the beginning of that interval (Supplemental Figure 1). A relative survival ratio of at least 1 means patient mortality does not exceed that of the general population. Although there is some variability in the estimates, especially for the later times, relative survival ratios approach 1 at 10–15 years for TT1, but this occurs earlier, at 5-10 years, for TT2+Thal and TT3a. A parametric mixture cure model (45) was used to estimate PFS and CRD for each protocol, overall and by GEP-70 risk from baseline, as well as from a 5 year landmark for all patients. The general idea behind the model is that there are two groups, those that are at risk for the event of interest and those that are not. The combined survival probability is represented as a mixture of the survival probabilities for these two groups. Mathematically, the model states that the PFS or CRD curve, \( S(t) \), is given by \( S(t) = p + (1 - p) S_1(t) \), where \( p \) is the cured fraction (long-term progression- or relapse-free survivors), and \( S_1(t) \) is the curve for the remaining fraction. In our models, \( S_1(t) \) was assumed to follow a Weibull distribution. The cure model fit the data well and provided cure-fraction estimates that increase with later protocols and when examined from baseline and a 5-year landmark (Supplemental Figure 2). Plateaus for both PFS- and CRD-based cure fractions emerged at 10 years in low-risk CMM and at 5 years in high-risk CMM (Supplemental Figure 3). Numeric data are presented for all patients in Table 1 (regardless of GEP risk). PFS-based cure-fraction estimates increased significantly with successive TT trials: 9% in TT1, 16% in TT2–Thal, 25% in TT2+Thal, and 33% in TT3a (\( p=0.04 \)); CRD-based cure-fraction estimates were 18%, 28%, 36%, and 49%, respectively (\( p=0.17 \)). When a 5-year landmark was applied to exclude early myeloma-related events, PFS-based cure fraction estimates were 28% in TT1, 39% in TT2–Thal, 51% in TT2+Thal,
and 70% in TT3a (p<0.001); in this setting, CRD-based cure fraction estimates were 32%, 47%, 56%, and 75%, respectively (p=0.007).

Is minimal residual disease (MRD) negativity an essential element for cure?

We have applied a sensitive 8 color flow cytometric approach for the assessment of MRD (19, 28). In contrast to published reports focusing measurements on a landmark of 100 days after transplant, we examined MRD status in >10yr progression-free survivors of TT1 and TT2 protocols. In TT1, 35 surviving patients of the original 231 have been followed for at least 17 years; 21 remain progression-free, and one each was MRD- and MRD+ among the 2 patients tested. In the case of TT2, all 258 currently surviving patients of initially 668 have been followed for at least 10 years. Of 175 patients remaining progression-free, MRD testing was performed in 83 patients along with reexamination of clinical CR status. Table 2 depicts, for combined TT1 and TT2 data, the relationship between clinical CR and MRD status. Among 85 patients, 68 qualified for CR of whom 64 proved to be MRD-negative; among 17 patients not in CR, 14 were deemed MRD-positive and 3 MRD-negative. Collectively, these data indicate that the majority of long-term CR patients also qualified for MRD-negativity. A minority of patients had discordant readings between CR and MRD designations, 4 CR’s were MRD-positive and 3 MRD-negative patients did not fulfill clinical CR criteria. In light of persistence of MRI-defined focal lesions in clinical CR and MRD negativity, further refinements of “global” patient CR and MRD designations are anticipated.

While most investigators consider CR a prerequisite for long-term PFS and cure (46-52), we reported previously that PFS and OS were not compromised by lack of CR in patients with documented preceding AMM (53) and those with MGUS-like CMM based on GEP (54, 55). However, CR was crucial for long term PFS and OS in high risk CMM (56). We also addressed the importance of a critical duration of CR for PFS durability (57). Best outcomes were observed when CR was sustained beyond a 3-year landmark. Those failing to achieve CR but remaining progression-free during this time frame fared better than patients attaining and losing CR. With long-term follow up available in TT1 and TT2 trials, we examined the role of CR for long term prognosis from a 2-year landmark (Figure 6). While PFS was superior in patients remaining in CR
at 2 years, plateaus were also apparent among non-CR patients. Thus, while a critical early event in terms of the degree of tumor mass reduction, CR is not essential for long-term disease control in all cases.

**In search of an early surrogate marker for cure in CMM**

It is widely recognized that MM cells engage the bone marrow micro-environment for their survival and expansion and, through these interactions with stroma, receive signals that are responsible for cell adhesion-mediated drug resistance (58). Additional data suggest that the progression from MGUS to AMM to CMM is mediated via a change in stromal cell behavior, possibly mediated via an angiogenic switch, the underlying mechanism of which is under investigation (59, 60). We, therefore, compared GEP signatures of whole bone marrow biopsies from healthy donors and from patients with MGUS, AMM and CMM in CR or at baseline prior to therapy (Figure 7). A median 37-gene score was highest in CMM at baseline and decreased progressively in comparisons of AMM to MGUS to CR and normal donors (Figure 7A); the 37-gene score had a wider spread in CR patients than in healthy volunteers. GEP data of bone marrow biopsies from patients who achieved and remained in CR were compared with those of age- and gender-matched healthy donors. Preliminary data indicate that normal-like GEP signatures can be achieved during CR and are associated with outcomes superior to those associated with MM-like signatures (Figure 7B).

**Challenges and opportunities for developing novel curative trials in CMM**

Most of our cured patients have CMM that is classified by the GEP70 model as low risk and have been followed for at least 10 years. A review of mature trials that used novel agents without or with transplantation shows that their follow-up times are not yet sufficient for cure plateaus to have emerged (61, 62). High CR rates approaching or even exceeding those reported after transplants have been reported after novel agent combinations without transplants, especially for combination regimens of carfilzomib, lenalidomide, and dexamethasone (18) and of carfilzomib, cyclophosphamide, and dexamethasone (63). However, it is not yet clear whether CR achieved by these
therapies is as durable as that induced with transplant-supported high-dose melphalan. We suggest that melphalan-type therapy may target MM stem cells with aggressive clinical behavior and thus prevent or at least reduce late relapse, thus, induce long-lasting benefits with cure potential but that non-genotoxic drugs may require chronic therapy. Several more years of follow-up will be required to answer this important question.

Our data show that for patients with high-risk CMM, novel therapies are needed. Even with TT approaches, median PFS of these patients is only 2 years although a small cure fraction of approximately 15% does emerge at 5 years. Work is in progress to determine whether earlier disease progression in high-risk CMM may be linked to a lower depth of CR as judged by sensitive MRD detection strategies.

In reflecting on the failure of our TT approach to advance clinical outcomes in high-risk MM, we considered the role of “cytokine storms” ensuing after chemotherapy or autologous transplants for steady state normal hematopoiesis to be established. By exerting stimulatory effects also on MM cells, such cytokine release may contribute to MM survival and disease escape. Our recently published metronomic therapy using low doses of cytotoxic agents (doxorubicin, cisplatin) in combination with bortezomib, thalidomide, and dexamethasone was exquisitely devoid of bone marrow toxicity (64). Extending treatment to 28 days, we offered such therapy to 10 transplant-ineligible newly diagnosed patients with high-risk CMM. Treatment was well tolerated and brought about CR in 5 patients at the conclusion of one cycle, lasting unmaintained for up to 8 months (unpublished). In light of poor outcomes in high-risk CMM, we are following 1-cycle CR patients closely to determine the length of benefit and especially whether “down-grading” from GEP-defined high- to low-risk can be demonstrated.

Exome sequencing revealed a prevalence of K-RAS, N-RAS, and BRAFF mutations especially in advanced CMM (9, 10, 32, 33). Using the MEK inhibitor trametinib (65), we have shown impressive preliminary response and have followed several patients with extra-medullary MM for 8+ months without recurrence. Applying such targeted therapies upfront in high-risk CMM will reveal whether durable CR’s can be attained or whether, due to ITH, relapses are inevitable. We are investigating
whether, due to cross-talk among MM sub-clones, the efficacy of targeted therapies may also favorably affect off-target sub-clones.

Conclusions

The data presented here allow us to conclude that CMM has finally joined the “club” of curable malignancies. The assessment of curability, at least in the context of melphalan-based auto-transplants, requires a minimum follow-up of 10 and more years. Based on CRD at baseline and a 5-year landmark, TT3a effectuated cure fraction estimated of almost 50% and 75%, respectively, pertaining to the majority of patients with GEP-defined low-risk MM. Among the 15% of patients with high-risk CMM, only 15% were estimated cured with an earlier plateau apparent at 5 years.

High CR rates comparable to those achieved with more toxic autotransplant-supported high-dose melphalan have recently been reported with the sole use of novel-agent combinations. Whether these different therapeutic approaches result in equally durable CR, longer follow up is required. In the interim, we are concerned about prematurely abandoning transplants in favor of therapy solely based on novel agents. In light of the stagnant clinical outcomes in high-risk CMM, we strongly endorse novel agent trials specifically for patients with GEP-based high-risk CMM where readily interpretable outcome results would be available within 2 to 3 years. For low-risk CMM, the availability of surrogate endpoints for cure would enormously aid in designing clinical trials aimed at developing less toxic therapy. Such approaches would include individualized therapy content and duration, taking into consideration GEP-based molecular subgroups potentially benefiting from different novel agents. Thus, the MS molecular subgroup is no longer considered high-risk when bortezomib is included in its management (42). Candidate surrogate methods include flow cytometric analysis of MRD and GEP analysis of whole bone-marrow biopsies, the latter encompassing MM cells and the microenvironment. Results of either method can be complicated by MRI- and PET-defined focal lesions or macro-focal growth patterns in many CMM patients, which can persist years after onset of clinical CR. Therefore, it may be necessary for standard iliac crest sampling to be complemented by focal lesion examinations. Alternatively, using mi-RNA (66) or exosome analysis (67) of peripheral blood may
emerge as a more powerful and quantitative approach, based on the notion of metastatic trafficking of MM cells between bone marrow and extra-medullary sites (68). Although ITH is widely appreciated as the major obstacle to cure, our data indicate curability in both low- and high-risk CMM when applying TT principles.

Acknowledgement

The authors wish to appreciate the dedication of the Myeloma Institute’s staff for caring for so many patients and their families with utmost dedication. We are indebted to our referring physicians. The Institute’s research nurses and data managers have been critical to the execution of our clinical research efforts.

As we celebrate cure in myeloma, we remain humble in our recognition of the many lives lost in heroic battles with end-stage myeloma. We are committing ourselves to improve clinical outcomes in high-risk myeloma and to reducing treatment-related complications.

The senior author wishes to acknowledge his mentor, Dr. Emil J Freireich, for having inspired the curability concept also for myeloma more than 25 years ago.

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Author Contributions

BB conceptualized and wrote paper, was principal investigator of protocols, enrolled and treated patients.

AM performed statistical analyses.

FVR enrolled and treated patients and discussed results.

JE discussed work and helped design clinical trials.

GM helped write paper.
JC conceptualized statistical analyses.

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References


Table 1: Cure fraction estimates by protocol, employing progression-free survival (PFS) and complete response duration (CRD)

A: From start of therapy

<table>
<thead>
<tr>
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<th>PFS N</th>
<th>Cure Fraction</th>
<th>CRD N</th>
<th>Cure Fraction</th>
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<td>231</td>
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<td>TT2 +Thal</td>
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<td>200</td>
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<tr>
<td>TT3a</td>
<td>303</td>
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<td>189</td>
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B: From 5-yr landmark

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<th>Cure Fraction</th>
<th>CRD N</th>
<th>Cure Fraction</th>
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Table 2: Correlation between clinical CR and MRD status

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<tr>
<td>Total</td>
<td>17</td>
<td>68</td>
<td>85</td>
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Figure 1: Components of Total Therapy trials TT1, TT2 and TT3a

<table>
<thead>
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<th>TT1</th>
<th>TT2 (randomization Thal vs No Thal)</th>
<th>TT3A</th>
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<td>V-DTPACE</td>
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<td>Dex + IFN± Thal</td>
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<td></td>
<td>Monthly VDT</td>
<td>Thal + Dex</td>
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Figure 2: Survival Estimates by Protocol
Overall and progression-free survival curves (A-D) show progressive narrowing with transition from TT1 to TT2-Thal to TT2+Thal to TT3a. Progressive improvement between protocols in overall and progression-free survival is apparent (E, F).
Figure 3: Response and Progression Estimates by Protocol

The cumulative incidence of complete response (A) translates into longer complete response duration (B). Of note, despite similar times of onset of CR in TT2+Thal and TT3a, CR duration is far superior with TT3a, suggesting that a deeper level of CR was effectuated. With transition to later protocols, the slopes of time to progression (C) and time to relapse from complete response (D) progressively flatten and reach lower plateaus.
Figure 4: Progression Estimates by Protocol and GEP-70 Risk
Progression-Free Survival and Time to Progression are analyzed according to plasma-cell gene expression profiling-based low and high risk subsets. Common to all endpoints examined, plateaus are reached earlier at approximately 5yr in high risk (B:PFS, D:TTP) compared to 10yr in the majority of 85% of patients with low risk myeloma (A:PFS, C:TTP).
Figure 5: Response Estimates by Protocol and GEP-70 Risk
Cumulative Incidence of Complete Response (CRI) and Complete Response Duration are analyzed according to plasma-cell gene expression profiling-based low and high risk subsets. Common to all endpoints examined, plateaus are reached earlier in high risk (B:CRI, D:CRD) than patients with low risk myeloma (A:CRI, C:CRD).
Figure 6: Progression-free Survival by CR Status at 2 Year Landmark by Protocol
Patients considered here were alive and progression-free at the 2 year landmark. Plateaus are seen in patients achieving CR and lesser responses prior to the 2 year landmark (A: TT1, B: TT2-Thal, C: TT2+Thal).
Gene expression profiling of whole bone marrow biopsy material encompasses both hematopoietic and bone marrow micro-environmental tissues. In the case of myeloma and precursor conditions, myeloma plasma cells co-exist in the biopsy material with normal hematopoietic and stromal elements. Marked differences in the 37-gene score were noted between CMM, AMM, MGUS, CR, and Normal Donors (A). Myeloma patients qualifying for complete response (CR) status and whose bone marrow biopsy becomes normal donor-like ("normalization") enjoy superior CR duration than their counterparts not qualifying for normalization. CR Duration according to "Normalization" of bone marrow biopsies of patients with MM was compared (B).

**Figure 7: Gene Expression Profiling of Bone Marrow Biopsy Material**
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