CLINICAL TRIALS

Comment on Harousseau et al, page 3743

No longer the poor relations

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Re-analysis of the VISTA trial of bortezomib in frontline therapy for transplant-ineligible myeloma patients has demonstrated that achieving a complete response is statistically correlated with a better outcome.

In the 1938 edition of the *British Encyclopaedia of Medical Practice*, a page within the chapter on leukemia is devoted to a description of the clinical and hematologic differences between plasma cell leukemia and multiple myelomatosis. The observations made remain valid to this day. Unfortunately, to a significant degree, so does the prophetic final sentence: “The prognosis is hopeless, whether the condition is regarded as myelomatosis or leukemia.”

Subsequent to this publication, no relevant progress in the treatment of myeloma was made until the synthesis in the 1950s, and clinical evaluation the following decade, of the alkylating agent melphalan. Its use was associated with a disease response in approximately 50% of patients and a modest prolongation in survival for those responding patients. It was then 3 decades before the landmark publication by Attal et al on behalf of the Intergroupe Francophone du Myélome demonstrated for the first time in a randomized clinical trial that high-dose chemotherapy (HDT) with autologous stem cell transplantation (ASCT) support resulted in a statistically significant prolongation of survival when compared with multi-agent conventional-dose chemotherapy. A number of subsequent studies confirmed these observations and led not only to the gradual adoption of ASCT as frontline therapy for “transplant-eligible” myeloma patients but also to 2 fundamental conceptual changes relating to the management of myeloma. First, it inspired investigators to seek clarification as to whether the attainment of a complete response (CR), a level of response previously rarely achieved, would, as would seem intuitive, be associated with a better patient outcome. And indeed it can really be no great surprise that a variety of subsequent studies, based on the use of HDT, did indeed confirm that the attainment of CR correlates with prolonged survival, as is the recognized paradigm in other hematologic malignancies.

Second, it led to the “dichotomization” of myeloma management, with patients being categorized early in their therapeutic course as either transplant-eligible or transplant-ineligible. The former then led to an explosion of activity examining new therapeutic strategies in myeloma, significantly fueled toward the end of the millennium by the incorporation of the “novel” therapeutics (thalidomide, lenalidomide, bortezomib) that were focused predominantly on the transplant-eligible population where the holy grail of achieving a CR was of demonstrable benefit. Although this more aggressive therapeutic philosophy has greatly benefited a significant minority of myeloma patients, the downside is that the more prevalent transplant-ineligible myeloma patients, to a large degree, have been left behind in what may be perhaps considered the somewhat anachronistic therapeutic milieu that accepts attainment of a “plateau phase” to be sufficient.

The results from the study by Harousseau et al in this issue of *Blood* have now unequivocally demonstrated that achieving a CR in the context of transplant ineligibility is likewise statistically correlated with a better outcome.

The authors have previously shown that upfront treatment with 9 cycles of VMP (bortezomib-melphalan-prednisone) is superior to 9 cycles of MP in terms of response rate and survival. With this analysis of the pooled outcome data from both arms of the original trial, they show that achieving a CR is associated with superior time to progression (TTP), time to next therapy (TNT), and treatment-free interval (TFI) when compared with achieving a partial response (PR). The study does not demonstrate that achieving a CR is correlated with superior overall survival. The authors
attributed this observation to the high likelihood of successful salvage approaches at the time of relapse and perhaps a reflection of the need for longer follow-up. Importantly, particularly for those clinicians of a more conservative mindset, is the approximate doubling in the duration of the TFI after the completion of induction therapy from approximately 15 to 30 months (see figure), an outcome that one could argue by itself justifies this more aggressive therapeutic approach. Also, of equal importance, is the observation that 39% of those patients that ultimately achieved a CR had a Karnofsky score of 70% or lower at study entry.

So why has it taken so long for such an observation to be made? It may simply be a numbers game. That is, in the absence of effective strategies, insufficient proportions of patients from previous studies attained CR and therefore a clinical benefit has not been evident. Conversely, it may be that the depth of response with VMP is greater than those responses achieved previously and it may be this factor that translates into the correlation with superior outcomes. The latter question will clearly not be answerable from the VISTA trial, but available limited molecular data certainly suggests that levels of response beyond what we currently define as a CR may correlate with further improvements in patient outcome. Whereas it is likely that investigators will be occupied for the best part of the next decade determining the impact of more robustly defined responses in myeloma and the optimal methods for identifying such responses, it is clear that, where feasible, a common therapeutic goal of attaining a state of minimal residual disease should be applied irrespective of transplant eligibility. Being defined as transplant-ineligible should no longer condemn a patient to being a poor relation in the paradigm informing the treatment of myeloma.

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REFERENCES


Comment on Hughes et al, page 3758

CML: how low can you go?

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The use of imatinib mesylate as a specific inhibitory treatment of the BCR-ABL tyrosine kinase has revolutionized the treatment of CML. Although results of treatment in patients in accelerated phase or blast crisis remain suboptimal, the rate of progression to advanced phase from chronic phase has dramatically been reduced such that approximately 90% of patients treated with imatinib at the time of diagnosis remain alive with follow-up that now approaches 8+ years. The results in chronic phase are not perfect, however, and intent-to-treat analyses of large cohorts of chronic-phase patients suggest that approximately 60%-65% of patients remain on imatinib therapy 5 years after initiation of treatment.

Monitoring of response is a critical feature of the management of chronic myelogenous leukemia (CML) and international consensus guidelines have been developed suggesting therapeutic end points that should be achieved after specific durations of therapy. It is generally accepted that at a minimum, patients should attain a complete cytogenetic response (CCyR) because there is almost no disease progression in patients in CCyR after 2-3 years of treatment. In this issue of Blood, Hughes and colleagues report on a subgroup of patients from the IRIS trial and emphasize the clinical value of achieving a greater and more rapid reduction in tumor burden termed “major molecular response” (MMR) as quantified by quantitative polymerase chain reaction (Q-PCR). MMR is defined as a 3-log reduction in BCR-ABL transcript number compared with a pretreatment baseline. Importantly, the “starting point” is not the value for an individual patient (which is usually not available), but rather represents the average results of initial transcript numbers as assessed in 3 research laboratories of

![Landmark analysis at 12 months of rate of progression to accelerated or blast phases according to level of molecular response (image is the middle panel of Figure 4 in the Hughes et al article).](image-url)
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