Evaluation and monitoring of response to therapy in multiple myeloma

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The treatment of myeloma has undergone major changes in the last decade.[1,2] The most significant advances in therapy include the use of tandem (double) autologous stem cell transplantation (ASCT) to improve overall survival in patients not achieving complete response (CR) or very good partial response with the first ASCT,[3,4] and new active agents namely, thalidomide,[5-9] bortezomib,[10,11] and lenalidomide.[12,13] However, none of these strategies appears to be curative. Each of the new active drugs identified so far produces responses as single-agents in only approximately one-third of patients with relapsed myeloma. Today, there are major challenges in determining the best way to incorporate new active agents into the overall treatment strategy, and the sequence in which various therapies are to be administered in order to obtain the best clinical results in terms of overall survival and quality of life. In addition, numerous new drugs are being evaluated in preclinical studies and clinical trials, alone and in combination with known active agents.[14,15] It is critically important that active agents are correctly identified in an efficient manner, but at the same time agents that have limited activity in myeloma are not incorrectly labeled as being *effective*. The evaluation and monitoring of response to the various therapeutic options that are available and being tested is therefore of major importance, and has significant implications for clinical practice and research.

Assessment of response in myeloma

Current response criteria stratify the extent of response to therapy (such as CR versus partial response) to judge the activity of a given drug or regimen, and define disease progression to allow calculation of end-points such as time to progression (TTP) and progression-free survival

(PFS). Such assessments are used to monitor effectiveness of therapy in clinical practice, identify new active agents in clinical trials, and to compare various therapeutic interventions. Unlike clinical practice in which clinicians use various parameters to make an informed judgment about whether a known active agent or regimen is effective in a given patient with myeloma, strict, reproducible and valid criteria are required for clinical trials. Response measures that can serve as adequate and accurate surrogates for overall survival are critically needed since survival outcomes in myeloma take years to assess and require an extraordinarily large number of patients in order to show statistically significant differences.

Current response criteria for myeloma

The most commonly used response criteria in myeloma are those of the European Group for Blood and Bone Marrow Transplant/International Bone Marrow Transplant Registry/American Bone Marrow Transplant Registry (*EBMT/IBMTR/ABMTR*),[16] Southwest Oncology group (SWOG),[17,18] Eastern Cooperative Oncology Group (ECOG),[19] and the Chronic Leukemia-Myeloma Task Force,[20] All of these criteria rely primarily on the serum and urine monoclonal (M) protein levels measured by electrophoresis to stratify response categories. The EBMT/IBMTR/ABMTR criteria, commonly referred to as the Bladé criteria,[16] are now increasingly accepted as the standard criteria for clinical trials. The incorporation of the Bladé criteria into most recent clinical trials has been of major significance since it has allowed more appropriate comparisons of response and progression rates across clinical trials and across various forms of therapy, although due to the usual risks attendant with any non-randomized comparison, such data should be primarily used for hypothesis-generation.

Limitations of existing response criteria

Although current response criteria have been invaluable and provide reproducible end-points that can be readily assessed, they suffer from some limitations. Certain limitations are related to the definitions used. For instance, the Bladé criteria[16] require specific reductions in M protein levels for each level of response, but the minimum baseline level of M protein that is required in the serum and urine to allow accurate response assessment is not specified. It is also not clear whether patients with detectable but *unmeasurable* levels of urine M protein (<100 mg/24 hours) need to have serial measurements of urine M protein and fulfill the urine criteria for response to be considered partial or minor responders.

Laboratory-based deficiencies in the assessment of response include the inherent limitations of electrophoretic measurements and immunofixation studies. How reliable is it to gate upon IgA M proteins migrating in the beta region on serum protein electrophoresis? What is the utility of quantitative immunoglobulin measurements by nephelometry? How reproducible are immunofixation studies? There is tremendous subjectivity in reporting these results, with potential for either over- or under-calling positive immunofixation studies, which can amount to faulty designations of either CR or relapse from CR.

The limitations discussed above though important are relatively minor compared to other more important problems with response assessment in myeloma (Table 1). For example, despite its utility in clinical practice such as distinguishing patients who may benefit from tandem transplantation from those who do not, the extent of response is a particularly poor in predicting the real outcome of interest, overall survival, in many clinical situations. Studies in newly diagnosed myeloma show that the extent of response (eg., response versus no response, CR versus lack of CR) to initial therapy- either in transplant or non-transplant candidates- may not predict overall survival outcome.[21-25] This maybe due to limitations of current initial therapy and the efficacy of salvage therapy, but does highlight one of the limitations of current response assessments.

Table 1. Some limitations of existing response criteria for myeloma.

Limitation	*Possible ways to improve the current criteria*
Relatively poor surrogate for overall survival	Incorporation of defined categories of more strictly defined complete response (CR) categories; eg.,immunohistochemical/ flow cytometric CR, free light chain CR, and molecular CR
Difficulties evaluating patients with non-secretory or oligo-secretory disease and patients with relapsed myeloma post-therapy with low monoclonal protein levels, often resulting in exclusion of these patients from major clinical trials.	Incorporation and validation of free light chain response criteria
Differences in definition of progression and relapse from CR	Use current definition of relapse from CR to calculate and report *disease-free survival* rates. For time to progression and progression-free survival rates, validate ability of such end-points to predict overall survival outcomes.
Commonly used, and clinically relevant sub-categories not uniformly defined	Categories of near CR or very good partial response need to be uniformly built in and reported given the clinical utility of such definitions, for example in choosing patients who may benefit from a second (tandem) transplant

There are also problems with the way disease progression is defined. The current definition of progression in the Bladé criteria[16] (a 25% increase in M protein) allows a higher event rate in a given time period than did the 50% increase required by the old Eastern Cooperative Oncology Group (ECOG) criteria. Though the more rapid achievement of progression end-points yields earlier trial completion, the significance of these events – especially in patients with low tumor burden – is yet to be determined. Adequate validation of time to progression end-points as true predictors of overall survival are clearly needed; otherwise we may mistakenly and prematurely conclude that we are improving the outcome for our patients.[26,27]

Finally, for the sake of simplicity and wide-spread test availability, some sacrifices have been made in stringency in terms of defining CR. For instance, although some older criteria had required the absence of monoclonal plasma cells, the current definition of CR does not require absence of monoclonal plasma cells but rather the reduction in plasma cells to less than 5% on bone marrow samples.[16] This naturally results in the contamination of a

subset of complete responders with normal polyclonal plasma cells in the marrow with those who still have monoclonal plasma cells easily detected by κ/λ immunostaining or immunofluorescence studies. The criteria need to be much more stringent, particularly since true CR may be a more accurate predictor of long-term outcome. In fact, the achievement of a true molecular CR may be the best surrogate for overall survival in myeloma. Evidence for this comes from earlier studies in which the more stringently one defines CR, response duration and post-response overall survival increase significantly.[28] In this issue of Haematologica, Sarasquete and colleagues (pages XXX) show that patients with CR who have minimal residual disease (MRD) by flow cytometric or allele specific oligonucleotide real time quantitative PCR (ASO-RQ-PCR) methods have significantly worse progression-free survival rates compared to patients with molecular or flow cytometric CR.[29]

Monitoring of response

The study by Sarasquete and colleagues and other studies like it[30] go to the heart of what may be of critical importance in the outcome of patients with myeloma—true molecular CR. Though there are increasing options available to achieve complete or near complete responses with combinations of drugs and transplantation, are we anywhere near cure? Despite the achievement of molecular CR in 46% of Sarasquete's cohort, there was no plateau in survival. Should treatment decisions be made based on the presence or absence of molecular CR? Should patients in true CR be assessed periodically by molecular or flow cytometric methods to allow early detection of MRD? Future studies will need to address these issues.

Although the authors conclude that MRD evaluation in their study by ASO-RQ-PCR was not of major advantage compared to flow cytometric methods, their study is underpowered to detect even major differences in outcome. In addition, the data are confounded by two design problems. First, more than half of the patients were not analyzed due to technical difficulties. Second, patients were not uniformly treated. Those who did not achieve CR by immunofixation were subjected to either another autologous or a non-myeloablative transplant, altering their outcome by introducing additional potential benefit (second transplant) and risk (treatment-related mortality). The authors' concept is, however, valid and so we would recommend larger studies to continue to testing the hypothesis that a molecular CR is the ideal endpoint of current myeloma therapy.

Future directions

As discussed above the definition of CR needs to be improved. Future studies need to determine whether molecular CR using complex as methods such ASO-RQ-PCR is important for patient care or whether absence of monoclonal plasma cells by flow cytometry or other comparable methods can be adequate. The assessment of molecular CR in myeloma is in the nascent stage and it is likely that any new response criteria will have to be updated and validated on a continuous basis to keep up with the pace of discovery.

Studies are also needed to determine the role of the serum free light chain assay (FLC) in defining response. The FLC assay has become widely available, and due to its high sensitivity allows measurement and monitoring of κ and λ free light chain levels even in most patients with non-secretory myeloma.[31-34] The development and validation of standard response criteria using the serum FLC assay can allow inclusion of a significant proportion of patients in clinical trials who are currently either excluded based on low serum and urine M protein levels or are followed with frequent serial bone marrow biopsies. Moreover, since the FLC assay is highly sensitive, CR based on normalization of the serum FLC ratio may prove to be a more stringent definition that could predict survival outcomes better than current criteria. We have proposed a 50% decrease in the mathematical difference between the *involved* (affected) and *uninvolved* (opposite) FLC level as a definition for partial response (provided the baseline *involved* FLC level is at least 100 mg/L) in patients who do not have measurable levels of serum and urine M protein levels; CR would require normalization of the FLC ratio to the normal range of 0.26-1.65.[35] Such criteria, however, also need validation.

The International Myeloma Working Group is currently in the process of developing response criteria that will incorporate many of the changes discussed above and also attempt to correct other deficiencies described earlier in existing criteria.

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References

1. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med 2004; 351:1860-73.
2. Anderson KC. Multiple myeloma: how far have we come? Mayo Clin Proc 2003;78:15-7.
3. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349:2495-502.
4. Cavo M, Cellini C, Zamagni E, Tosi P, Cangini D, Tacchetti P, et al. Superiority of double over single autologous stem cell transplantation as first-line therapy for multiple myeloma. Blood 2004;104:155a[Abstract 536].
5. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565-71.
6. Kumar S, Gertz MA, Dispenzieri A, Lacy MQ, Geyer SM, Iturria NL, et al. Response rate, durability of response, and survival after thalidomide therapy for relapsed multiple myeloma. Mayo Clin Proc 2003;78:34-9.
7. Richardson P, Schlossman R, Jagannath S, Alsina M, Desikan R, Blood E, et al. Thalidomide for patients with relapsed multiple myeloma after high-dose chemotherapy and stem cell transplantation: results of an open-label multicenter phase 2 study of efficacy, toxicity, and biological activity. Mayo Clin Proc 2004;79:875-82.
8. Rajkumar SV, Blood E, Vesole DH, Fonseca R, Greipp PR. A randomized phase III clinical trial of thalidomide plus dexamethasone versus dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2005; (in press).
9. Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini D, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicin dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood 2005;106:35-9.
10. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609-17.
11. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005; 352:2487-98.
12. Richardson PG, Schlossman RL, Weller E, Hideshima T, Mitsiades C, Davies F, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 2002; 100: 3063-7.

13. Rajkumar SV, Hayman SR, Lacy MQ, Dispenzieri A, Geyer SM, Kabat B, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005;Aug 23:[Epub ahead of print].
14. Richardson PG, Mitsiades CS, Hideshima T, Anderson KC. Novel biological therapies for the treatment of multiple myeloma. Best Pract Res Clin Haematol 2005;18:619-34.
15. Hideshima T, Bergsagel PL, Kuehl WM, Anderson KC. Advances in biology of multiple myeloma: clinical applications. Blood 2004;104:607-18.
16. Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115-23.
17. Alexanian R, Bonnet J, Gehan E, Haut A, Hewlett J, Lane M, et al. Combination chemotherapy for multiple myeloma. Cancer 1972;30:382-9.
18. McLaughlin P, Alexanian R. Myeloma protein kinetics following chemotherapy. Blood 1982;60:851-5.
19. Oken MM, Kyle RA, Greipp PR, Kay NE, Tsiatis A, Gregory SA, et al. Complete remission induction with combined VBMCP chemotherapy and interferon (rIFNα2b) in patients with multiple myeloma. Leuk Lymphoma 1996;20:447-52.
20. Anonymous. Proposed guidelines for protocol studies. I. Introduction. II. Plasma cell myeloma. III. Chronic lymphocytic leukemia. IV. Chronic granulocytic leukemia. Cancer Chemother Rep 3 1973;4:141-73.
21. Oivanen TM, Kellokumpu-Lehtinen P, Koivisto AM, Koivunen E, Palva I. Response level and survival after conventional chemotherapy for multiple myeloma: a Finnish Leukaemia Group study. Eur J Haematol 1999;62:109-16.
22. Durie BG, Jacobson J, Barlogie B, Crowley J. Magnitude of response with myeloma frontline therapy does not predict outcome: importance of time to progression in southwest oncology group chemotherapy trials. J Clin Oncol 2004; 22: 1857-63.
23. Kumar S, Lacy MQ, Dispenzieri A, Rajkumar SV, Fonseca R, Geyer S, et al. High-dose therapy and autologous stem cell transplantation for multiple myeloma poorly responsive to initial therapy. Bone Marrow Transplant 2004;34:161-7.
24. Singhal S, Powles R, Sirohi B, Treleaven J, Mehta J. Response to induction chemotherapy is not essential to obtain survival benefit from high-dose melphalan and autotransplantation in myeloma. Blood 2001;98:816a[Abstract 3390].
25. Rajkumar SV, Fonseca R, Dispenzieri A, Lacy MQ, Witzig TE, Lust JA, et al. Effect of complete response on outcome following autologous stem cell transplantation for myeloma. Bone Marrow Transplant 2000;26:979-83.
26. Goodman M. First, do no harm; second, make sure you are doing some good. J Clin Oncol 2005;23:1045-6.
27. Cannistra SA. The ethics of early stopping rules: who is protecting whom? J Clin Oncol 2004;22:1542-5.
28. Kyle RA, Leong T, Oken MM, Kay NE, Van Ness B, Greipp PR. The effect of complete response (CR) on survival in an ECOG phase III trial for multiple myeloma. Blood 1998;92 Suppl 1:319a[Abstract 1310].
29. Sarasquete ME, Garcia-Sanz R, Gonzalez J, Martinez D, Mateo G, Martinez P, et al. Minimal residual disease monitoring in multiple myeloma patients achieving complete response after autologous stem cell transplantation: a comparitive study between ASO real time quantitative PCR and flow cytometry. Haematologica 2005;90:1365-72.
30. Tricot G, Carrabba M, Barlogie B, Epstein J, Shaughnessy J, Corradini P. High Frequency of molecular remissions (m-CR) in multiple myeloma patients achieving a hematologic complete remission (CR) on total therapy II (TT-2). Blood 2004; 104:267a[Abstract 933].
31. Katzmann JA, Clark RJ, Abraham RS, Bryant S, Lymp JF, Bradwell AR, et al. Serum reference intervals and diagnostic ranges for free κ and free λ immunoglobulin light chains: relative sensitivity for detection of monoclonal light chains. Clin Chem 2002;48:1437-44.
32. Rajkumar SV, Kyle RA, Therneau TM, Melton III LJ, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance (MGUS). Blood 2005;106:812-7.
33. Bradwell AR, Carr-Smith HD, Mead GP, Harvey TC, Drayson MT. Serum test for assessment of patients with Bence Jones myeloma. Lancet 2003;361:48991.
34. Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, Bradwell AR. Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. Blood 2001;97:2900-2.
35. Rajkumar SV, Kyle RA. Conventional therapy and approach to management. Best Pract Res Clin Hem 2005;18:585-601.