International uniform response criteria for multiple myeloma


New uniform response criteria are required to adequately assess clinical outcomes in myeloma. The European Group for Blood and Bone Marrow Transplant/International Bone Marrow Transplant Registry criteria have been expanded, clarified and updated to provide a new comprehensive evaluation system. Categories for stringent complete response and very good partial response are added. The serum free light-chain assay is included to allow evaluation of patients with oligo-secretory disease. Inconsistencies in prior criteria are clarified making confirmation of response and disease progression easier to perform. Emphasis is placed upon time to event and duration of response as critical end points. The requirements necessary to use overall survival duration as the ultimate end point are discussed. It is anticipated that the International Response Criteria for multiple myeloma will be widely used in future clinical trials of myeloma.

Keywords: myeloma; response criteria; staging; survival duration; uniform criteria; clinical outcomes

Introduction

There is an increasing need for widely accepted, reproducible criteria to evaluate response in multiple myeloma.1,2 Several different systems are currently in use, but are not exactly comparable. For example, the US cooperative groups ECOG and SWOG have differing systems, as do several European groups, such as the MRC (UK)3 and the IFM (France).4 In addition, the European Group for Blood and Bone Marrow Transplant/International Bone Marrow Transplant Registry/American Bone Marrow Transplant Registry (EBMT/IBMT/ABMTR) developed widely used criteria, commonly referred to as the EBMT criteria.5 However, as discussed below, there is a need to update prior criteria.

The need for new uniform response criteria has been triggered by several factors (Table 1). The most pressing need is for criteria that facilitate precise comparisons between new treatment strategies. Better criteria are also required for use in the clinic at the individual patient level. In this setting, clarification of complete response (CR) is particularly important. As more active agents are available, there is a need to assess not just if response has occurred, but the exact magnitude of response. There is increased awareness of the distinction between surrogate end points such as reduction in M-component level and more clinical end points such as recovery of functional status or organ function, length of response and overall survival duration.6

Many of the commonly used criteria do not define CR stringently. In the EBMT criteria, CR does not require absence of monoclonal (M) plasma cells, but rather the reduction in plasma cells to 5% or less on bone marrow samples. 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 M plasma cells. The latter are easily detected by kappa/lambda immunostaining or by immunofluorescence studies using flow cytometry. Specific categories of CR with varying degrees of stringency allow greater precision in the definition of CR, enable comparison of the efficacy of various treatments including novel agents and can permit the detection and monitoring of relapse more accurately. Existing criteria lack sufficient detail, which as a result allows substantial investigator discretion, and leads to inaccuracies in the estimated response rate. For example, the EBMT criteria require specific reductions in M-protein levels for each category of response, but the minimum level of M-protein that is required in the serum and urine to allow accurate response assessment is not specified. Similarly, it is not clear from prior criteria how patients with ‘unmeasurable’ levels of urine M-protein should be monitored for response evaluation.

Finally, present criteria allow limited assessment of response in patients with oligo-secretory or non-secretory myeloma.7 Response in these patients can now be assessed using the sensitive serum free light-chain (FLC) assay (Freelite, Binding Site). Incorporation of the serum FLC assay into the response criteria for myeloma allows inclusion and evaluation of these patients in clinical trials.
Table 1  Rationale for the development of uniform response criteria

- Facilitate precise comparisons of efficacy between new treatment strategies in trials
- Incorporation of the serum FLC assay to include assessment of patients with oligo-secretory and non-secretory disease
- Stricter definitions for CR
- Provide clarifications, improve detail and correct inconsistencies in prior response criteria

Abbreviations: CR, complete response; FLC, free light chain.

Development of new response and relapse criteria

The International Myeloma Working Group has developed new standard diagnostic criteria and the new International Staging System (ISS) for multiple myeloma, which are being widely accepted as the current standards for diagnosis and staging. The development of the new response criteria proposed in this manuscript started with a meeting of the International Myeloma Working Group (participants are listed at the end of the manuscript) during the 10th International Myeloma Workshop, Sydney, 10–14 April 2005. Based on the discussions and decisions made at this meeting, the criteria were formulated and drafted by two of the authors (BGD and SVR) and circulated to the members of the Working Group and revised. Final approval was made at a meeting of the International Myeloma Working Group at the Annual Meeting of the American Society of Hematology, Atlanta, GA, USA, December 2005 and subsequent reviews of this paper.

A summary of the important changes in the new criteria versus prior systems is provided in Table 2. It is important to point out that for patients with measurable M-protein levels in the serum and urine, the definitions of complete and partial response as well as disease progression match those used in the EBMT (Bladé) criteria. Therefore, although important clarifications are added, for all practical purposes, in trials that include only patients with measurable disease response rates and progression, estimates reported using the using the new International Myeloma Working Group criteria will be comparable to those using the EBMT criteria. This will allow easy comparison of rates reported in trials using the EBMT criteria with those using the new criteria. The most important changes in the new criteria are (1) addition of a new category of stringent CR that is of significant importance given rapid advances in therapy, (2) addition of response criteria for interpreting the serum FLC assay, which will enable numerous patients hitherto excluded from clinical trials for lack of measurable disease to enter and be evaluated on clinical trials, and (3) formal addition of a category of very good partial response (VGPR) to allow distinction of patients with excellent responses that may have outcomes similar to those of patients with partial response (VGPR) to allow distinction of patients with clinical trials, and (3) formal addition of a category of very good partial response (VGPR) to allow distinction of patients with clinical trials, and (3) formal addition of a category of very good partial response (VGPR) to allow distinction of patients with clinical trials, and (3) formal addition of a category of very good partial response (VGPR) to allow distinction of patients with

Table 2  Summary of similarities and specific changes introduced in the New Uniform Response Criteria compared to the EBMT/IBMTR Criteria

- For patients with measurable levels of serum and urine monoclonal protein levels, the criteria for CR, PR and progressive disease remain unchanged. (Tables 5 and 6)
- Clarification and revision of important practical details of response evaluation (Table 4)
  - Clarification of the ‘start time’ for duration of response evaluation
  - Requirement of >PR as response requirement for new drug trials
  - Allow use of quantitative immunoglobulin levels in patients in whom the M-protein measurements are unavailable or unreliable
- Introduction of new response categories (Table 5) sCR and VGPR
- Elimination of the minor response category
- Incorporation of response criteria for the serum FLC assay to enable assessment of response in patients with non- or oligo-secretory disease (Tables 5 and 6)
- Clarification that criteria for progressive disease (rather than criteria for ‘relapse from CR’) are to be used for calculation of time to progression and progression-free survival in patients who are in CR. Criteria for relapse from CR are to be used only if DFS is calculated and reported
- Introduction of new category of clinical relapse or progressive disease (Table 6)
  - Introduces clinical relapse as a new optional end point

Abbreviations: CR, complete response; DFS, disease-free survival; EBMT, European Group for Blood and Bone Marrow Transplant; FLC, free light chain; IBMTR, International Bone Marrow Transplant Registry; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Diagnostic criteria for multiple myeloma

The need for clear baseline diagnostic criteria cannot be overemphasized. Three recent publications from the International Myeloma Working Group incorporate recommended methods for diagnosis, baseline staging and prognostic classifications as well as disease subtype identification. With these systems, the features of patients entering clinical trials can be clearly delineated. Table 3 summarizes the diagnostic criteria for active myeloma.

Response categories

Changes in the M-component level are the principal indicators used for response evaluation. It is important to note that M-component is a surrogate marker and its use is accompanied by all the pitfalls that can potentially detract from such use including variations in marker synthesis, metabolism or release as well as myeloma cell heterogeneity with respect to M-component production. The major response categories include CR, partial response (PR), stable disease (SD), progressive disease (PD) and relapse from CR (see Tables 5 and 6).

Additional subcategories have been used by a number of investigators. The subcategories of near complete response (nCR) and VGPR have been integrated into the new criteria under one single category termed ‘VGPR’. Importantly, the term ‘stable disease’ is not recommended for use as a measure of treatment efficacy; instead time to progression (TTP) and response duration estimates (see below) should be used in instances when the stability of disease with a particular therapy needs to be highlighted. TTP is calculated from the start of treatment and includes all patients entering the trial. Duration of response (DOR) is calculated from the time of first recorded achievement of a particular response level, that is, PR, VGPR, CR or sCR (see Table 5), and includes only responding patients. Although documentation of response requires a confirmatory measurement, the start time for DOR is the first date at which response was noted.
bone disease.

respectively if they have documented amyloidosis or 'myeloma with documented LCDD,' deposition disease (LCDD) should be classified as 'myeloma with

cells; these patients are referred to as having 'non-secretory myeloma'.

izing of serum FLC ratio is a stricter indicator of CR, and may closely monitor laboratory variation. 16 Strict guidelines are in the future, given its recently reported prognostic value in be useful in the prognostic and response evaluation of patients required with regard to usage times for the serum FLC assay kits. 16

FLC assay levels below 10 mg/dl (or 100 mg/l). Third, although some cases of IgA myeloma) for routine M-protein quantitation during therapy, then quantitative immunoglobulin levels on nephelometry or turbidometry can be accepted. However, this must be explicitly reported, and only nephelometry can be used for that patient to assess response and S.P.E. and nephelometric values cannot be used interchangeably.

Urine M-protein measurement is estimated using 24-h U.P.E. only. Random or 24-h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended Definitions of measurable disease

Response criteria for all categories and subcategories of response except CR are applicable only to patients who have 'measurable' disease defined by at least one of the following three measurements: Serum M-protein > 1 g/dl (> 10 gm/l100 g/l) Urine M-protein > 200 mg/24 h Serum FLC assay: Involved FLC level > 10 mg/dl (> 100 mg/l) provided serum FLC ratio is abnormal

Important aspects of response assessment

Table 4 summarizes important practical details in response assessment. Two specific points must be emphasized. Firstly, checking the M-component level at each cycle during induction is critically important in the evaluation of novel therapies to determine the speed of response, which may have clinical implications. For example, with several new regimens, response occurs rapidly and can be substantial within 1–2 months. 12, 13 The second point is that the new criteria eliminate the need for consecutive confirmations 6 weeks apart currently required for response testing. A D.O.R of 6 weeks does not carry major clinical significance and is not a surrogate for durability of response. The main concern is to eliminate laboratory or other error; this can be carried out by the requirement of a confirmatory test at any time following the first test provided it is before any new/non-protocol therapy. The importance of response, that is, its durability, should be highlighted by reporting data on T.T.P and D.O.R. Thus plateau phase can be documented by indicating the T.T.P and/or D.O.R. 1

Three aspects pertaining to the serum FLC assay deserve emphasis. First, the serum FLC assay (Freetite, The Binding Site, Birmingham, UK) is a highly sensitive marker of light chains in circulation that are unbound to intact immunoglobulin, and the FLC ratio is an excellent indicator of clonality. 14 Thus, normalizing of serum FLC ratio is a stricter indicator of CR, and may correspond with extended response duration. 15 (Kumar S et al. Blood 2005; 106: 9712.) In patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Second, in order to minimize chance of error, FLC response is not assessable for patients who start with low baseline serum FLC assay levels below 10 mg/dl (< 100 mg/l). Third, although the serum FLC assay is a very reliable test, it is important to closely monitor laboratory variation. 16 Strict guidelines are required with regard to usage times for the serum FLC assay kits. It should also be noted that serum FLC assay testing might be useful in the prognostic and response evaluation of patients who also have a measurable serum and/or urine M-component in the future, given its recently reported prognostic value in M-gammopathy of undetermined significance (MGUS). 17

Table 4 Practical details of response evaluation

Laboratory tests for measurement of M-protein

Serum M-protein level is quantitated using densitometry on S.P.E except in cases where the S.P.E is felt to be unreliable such as in patients with IgA monoclonal proteins migrating in the beta region. If S.P.E is not available or felt to be unreliable (e.g., in some cases of IgA myeloma) for routine M-protein quantitation during therapy, then quantitative immunoglobulin levels on nephelometry or turbidometry can be accepted. However, this must be explicitly reported, and only nephelometry can be used for that patient to assess response and S.P.E and nephelometric values cannot be used interchangeably.

Urine M-protein measurement is estimated using 24-h U.P.E. only. Random or 24-h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended Definitions of measurable disease

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Response criteria for CR are applicable for patients who have abnormalities on one of the three measurements. Note that patients who do not meet any of the criteria for measurable disease as listed above can only be assessed for stringent CR, and cannot be assessed for any of the other response categories

Follow-up to meet criteria for PR or SD

It is recommended that patients undergoing therapy be tracked monthly for the first year of new therapy and every other month thereafter.

Patients with ‘measurable disease’ as defined above need to be followed by both S.P.E and U.P.E for response assessment and categorization

Except for assessment of CR, patients with measurable disease restricted to the S.P.E will need to be followed only by S.P.E; correspondingly, patients with measurable disease restricted to the U.P.E will need to be followed only by U.P.E Patients with measurable disease in either S.P.E or U.P.E or both will be assessed for response only based on these two tests and not by the FLC assay. FLC response criteria are only applicable to patients without measurable disease in the serum or urine, and to fulfill the requirements of the category of stringent CR

To be considered CR, both serum and urine immunoassays must be carried out and be negative regardless of the size of baseline M-protein in the serum or urine; patients with negative U.P.E values pretreatment still require U.P.E testing to confirm CR and exclude light chain or Bence–Jones escape

Skeletal survey is not required for assessment of response unless clinically indicated, but is recommended once a year in clinical practice; bone marrow is required only for categorization of CR, and for patients with non-secretory disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; S.P.E, serum protein electrophoresis; U.P.E, urine protein electrophoresis.

*For good clinical practice patients should be periodically screened for light chain escape with U.P.E or serum FLC assay.

The international Myeloma Working Grop Uniform Response Criteria

The International Myeloma Working Group Uniform Response Criteria are listed in Table 5. Under CR two categories are listed: CR and stringent (s.C.R). The CR category is available for widespread use and provides continuity with prior systems. However, s.C.R, the more stringent category, allows more
**Table 5** International Myeloma Working Group uniform response criteria: CR and other response categories

<table>
<thead>
<tr>
<th>Response subcategory</th>
<th>Response criteria</th>
</tr>
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<tbody>
<tr>
<td>sCR</td>
<td>CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence</td>
</tr>
<tr>
<td>CR</td>
<td>Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and &lt;5% plasma cells in bone marrow</td>
</tr>
<tr>
<td>VGPR</td>
<td>Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level &lt;100 mg per 24 h</td>
</tr>
<tr>
<td>PR</td>
<td>≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to &lt;200 mg per 24 h</td>
</tr>
<tr>
<td>SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)</td>
<td>Not meeting criteria for CR, VGPR, PR or progressive disease</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

Confirmation with repeat bone marrow biopsy not needed.

Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of >4:1 or <1:2.

The difficulties and nuances in evaluating myeloma-related events are well known. It is important to re-emphasize that myeloma must be the cause of events. Whatever additional testing is required to confirm myeloma relatedness is strongly encouraged. This may include magnetic resonance imaging, computed tomography and/or fluoro-18-deoxyglucose (FDG)/positron emission tomography (PET) imaging (Walker R et al. Blood 2004; 104: 217a, abs 758).
Clinical relapse requires one or more of:

- Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)
- Increase of >25% from baseline in:
  - Serum M-component and/or the absolute increase must be ≥0.5 g/dL
  - Urine M-component and/or the absolute increase must be ≥200 mg/24 h
- Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL.
- Bone marrow plasma cell percentage: the absolute % must be ≥10% if:
  - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
  - Development of hypercalcemia (corrected serum calcium ≥11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Relapse from CR (To be used only if the end point studied is DFS)

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<th>Relapse criteria</th>
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<tr>
<td>Progressive diseasea</td>
<td>Progressive Disease: requires any one or more of the following:</td>
</tr>
<tr>
<td>To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)</td>
<td>Increase of ≥25% from baseline in:</td>
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<td>- Serum M-component and/or the absolute increase must be ≥0.5 g/dL</td>
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Survival end points

End points such as PFS, TTP and DOR can predict ultimate overall survival (Tricot G et al. Blood 2004; 104: 265a, abs 926).6,20–22 Several different methods are used to calculate response duration and the impact of treatment.

- **PFS**: PFS is the time from start of the treatment to disease progression or death. This encompasses all patients and has been considered a surrogate marker for overall survival duration. This is the recommended method to present trial results.
- **Event-free survival (EFS)**: The definition for EFS depends on how ‘event’ is defined. In some studies, this can be the same as PFS. EFS can also include additional ‘events’ that are considered to be of importance besides death, including serious drug toxicity. EFS is not recommended for general use unless specifically defined, as confusion can arise about the details of additional ‘events’. PFS is preferred.
- **TTP**: This is the time from start of treatment to disease progression with deaths owing to causes other than progression not counted, but censored. This is a helpful method to assess the durability of treatment benefit.
- **Disease-free survival (DFS)**: DFS applies to patients in CR, and is measured from the start of CR to the time of relapse from CR. This parameter has limited value in myeloma at present.
- **DOR**: DOR applies to patients achieving at least PR by the criteria in Table 5, and is measured from start of achieving PR (first observation of PR before confirmation) to the time of disease progression, with deaths owing to causes other than progression not counted, but censored. This is an additional parameter for consideration in the assessment of new agents and/or new comprehensive treatment strategies. DOR and TTP are the recommended ways of establishing the durability of response.

Overall survival

Many recent myeloma trials have had response and/or TTP as the primary end points. However, overall survival and quality of life reflect the full impact of therapies. Several factors limit the use of overall survival as the ultimate end point.

- Over 5 years of follow-up are required to assess benefit.
- Initial response and TTP may or may not translate into overall survival benefit.
- New agents used as part of induction, consolidation/transplant and/or maintenance are frequently used at time of relapse in the ‘control’ (non-use) arm of trials. Thus the comparison is with early versus later use. There has been no widely accepted plan or framework to control for this.
Additional new agents are now being introduced, which can further impact outcome assessment.

The problems involved are illustrated by several trials. In a recent trial reported by the Arkansas group, thalidomide was used as part of the TT-2 in one arm of the trial and produced a significantly higher CR rate and disease-free interval. However, overall survival was not improved. But, it is important to note that 83% of patients not in the thalidomide arm received thalidomide at relapse. Thus, the study reflects an unplanned ‘early’ versus ‘later’ use of a therapeutic intervention, in this case thalidomide. In a more minor way, this was also an issue in the recently published results of the melphalan/prednisone (MP) versus MP thalidomide trial. New trial designs to evaluate survival duration must accommodate these types of complexity. These details are further discussed in a recent review.1

Conclusions

The response criteria outlined in this paper are expected to be used widely in future clinical trials of myeloma. The major new additions to the response criteria are categories of stringent CR, VGPR and incorporation of the serum FLC assay to evaluate patients with oligo-secretory disease. The criteria also clarify several inconsistencies in prior response criteria, make confirmation of response and disease progression easier to perform with less chance of deviations, and define time to event end points that are critical in the evaluation of outcome.

References

Response criteria for multiple myeloma
BGM Durie et al

Appendix A.

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Leukemia