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LEADING ARTICLE

Clinically relevant end points and new drug approvals for myeloma

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This manuscript summarizes the recommendations of the American Society of Hematology/US Food and Drug Administration Workshop on Clinical Endpoints in Multiple Myeloma, which brought together clinical investigators in multiple myeloma, the United States Food and Drug Administration, pharmaceutical companies, patient advocates and other concerned scientists and physicians to provide guidance, consensus and consistency in the definition of clinically relevant end points to expedite new drug approvals for multiple myeloma in the appropriate trial design settings. This manuscript will therefore be a most valuable resource to provide the framework for the design of appropriate clinical trial strategies for more rapid new drug approval in myeloma.
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Introduction

There is a major need to develop clearly defined end points to support claims of efficacy of therapies for multiple myeloma (MM). These end points need to be developed and utilized by investigators leading clinical trials in MM, with input from the United States Food and Drug Administration (FDA), pharmaceutical companies, patient advocates and other concerned scientists and physicians in the field. The goal is to provide guidance, consensus and consistency in the definition of clinically relevant end points that can expedite new drug approvals for MM in the appropriate trial design settings. The examples of recent new drug approvals in MM, including bortezomib, thalidomide and lenalidomide, illustrate the need for and success of early partnership of industry, academia, the FDA, the National Cancer Institute and patient advocates to expedite drug development in MM.[1,2] This manuscript summarizes and reviews the recommendations of the clinical investigator participants of the ASH™/FDA Workshop on Clinical Endpoints in MM committee. More information as well as slide presentations from the workshop can be found at www.hematology.org/policy/news/fda_workshop_multiple_myeloma.cfm.

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Assessment of response

The International Myeloma Working Group (IMWG) uniform response criteria for MM was recommended as a new standard for response criteria in registration trials (Table 1).[3] These criteria were developed with input from over 70 MM experts from around the world, with representation from the cooperative groups, and are now being incorporated into new clinical trials, with certain aspects (such as the serum-free light chain measurement) subject to validation in ongoing studies. In patients with measurable serum or urine M protein, the IMWG criteria are similar to the European Group for Blood and Marrow Transplant (EBMT) criteria[4] definitions for partial/complete response (CR) and progression. In addition, IMWG adds two new categories as follows: very good partial response (VGPR) and stringent CR category. Importantly, the use of the free light chain assay to assess response in patients with oligo-secretory MM has been proposed, which constitutes an important step since these patients traditionally have been excluded from clinical trials.

Minor response, as defined in the EBMT criteria (Table 2), is not included in the IMWG criteria but can indicate clinical benefit in patients with relapsed and/or refractory MM. For example, in a recent analysis of the APEX bortezomib trial, patients with minor response (MR) had longer time to progression (TTP) and overall survival (OS) than non-responders.[5] Although MR alone may not meet the threshold required for regulatory approval, it is an important indicator of drug activity in certain patient populations, and in particular for patients with relapsed and relapsed, refractory MM.

The definition of MM progression, as defined in the IMWG and EBMT criteria, is primarily biochemical; it does not delineate clinically meaningful progression in asymptomatic patients with monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM). In these patients, compelling clinically meaningful evidence of progression would be the development of end-organ damage definitely attributable to the clonal plasma cell proliferation. In patients with MGUS and SMM, the criteria indicating progression to active MM are listed in Table 2.

Baseline levels of M protein measurable for assessment of response in MM are defined as presence of serum M protein $\geqslant$1 g per 100 ml ($\geqslant$10 g l^{-1}) and/or urine M protein $\geqslant$200 mg per 24 h. When baseline levels are below these thresholds, reductions of 50% or greater cannot be reliably assessed and monitored in the laboratory. Serum-free light chain-based assessment of response has not yet been well validated; drug registration studies should restrict patient eligibility to those with 'measurable disease'.[3] Moreover, it is also recognized that ongoing refinement of response criteria and appropriate modification may occur as prospective studies validate aspects of the new response categories.

Table 1 International myeloma working group uniform response criteria for multiple myeloma[3]

Major response categories	*Response criteria*[a]
CR	No M protein on serum and urine immunofixation and Disappearance of any soft-tissue plasmacytomas and <5% plasma cells in bone marrow
VGPR	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ⩾90% or greater reduction in serum M protein plus urine M-protein <100 mg per 24 h
PR	⩾50% reduction of serum M protein and reduction in 24 h urine M-protein by ⩾90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable a ⩾50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ⩾50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ⩾30% In addition to the above criteria, if present at baseline, ⩾50% reduction in the size of soft-tissue plasmacytomas is also required
SD	Not meeting criteria for CR, VGPR, PR or progressive disease
PD	Increase of 25% from lowest response value in: Serum M protein (absolute increase must be ⩾0.5 100 ml) and/or Urine M-component (absolute increase must be ⩾200 mg/24 h) and/or Bone marrow plasma cell percentage (absolute % must be 10%) and/or Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg per 100 ml) 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 per 100 ml) that can be attributed solely to the plasma cell proliferative disorder

Abbreviations: CR, complete response; FLC, free light chain; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.
[a]All response categories (CR, sCR, VGPR, PR) require two consecutive assessments made at anytime before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments are not required to be confirmed by repeat testing.
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Table 2 Additional response criteria for specific disease stages[3,4]

Category	*Crtieria*
Minor response[a]	⩾25% but <49% reduction of serum M protein and reduction in 24 h urine M-protein by 50–89% which still exceeds 200 mg per 24 h In addition to the above criteria, if present at baseline, 25–49% reduction in the size of soft-tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progression to active myeloma[b]	Evidence of progression based on the IMWG criteria for progressive disease in myeloma and Any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder[c] Development of new soft-tissue plasmacytomas or bone lesions Hypercalcemia (>11 mg per 100 ml) Decrease in hemoglobin of ⩾2 g per 100 ml Rise in serum creatinine by 2 mg per 100 ml or more

Abbreviation: MR, minor response.
[a]Adapted from the European Group for Blood and Marrow Transplant (EBMT) criteria.[4]
[b]For use as progression end point in patients with MGUS or smoldering multiple myeloma.
[c]Adapted from the definition of clinical relapse in the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma.[3]

Assessment of patient reported outcomes

Patient reported outcomes (PROs) are an important end point to be considered for registration purposes since, in theory, they document changes in how patients feel and function. In MM, response with therapy is usually associated with improved PROs.[6] Moreover, improvement in PRO has been one of the main reasons why many physicians prefer early stem cell transplant in younger patients with MM.[7] The most specific disease-related type of PRO relevant to measures of clinical benefit in MM is alleviation of bone pain due to MM bone disease. Global quality of life scales that purport to measure functional well-being were not felt to be adequate for drug registration purposes, since they typically do not assess symptom domains specific to MM, they lack validity, and missing data elements are universal in studies to date. Also, they may reflect both symptom changes and treatment toxicity. MM-specific PRO tools are being developed by Eastern Cooperative Oncology Group (ECOG) and are being incorporated into new clinical trials, but they require further validation. Tools that assess one or more specific PROs that are of major importance and markers of clinical benefit in MM need to be refined and validated, and investigators will have to commit in obtaining complete data on their patients before PROs can be evaluated as primary end points for regulatory studies in MM, but further study is encouraged.

MGUS and smoldering (asymptomatic) multiple myeloma

MGUS is defined by serum monoclonal immunoglobulin concentration ⩽3 g per 100 ml, ⩽10% plasma cells in the bone marrow (BM), and no anemia, hypercalcemia, lytic bone lesions, renal insufficiency or other end-organ damage related to the proliferation of the monoclonal plasma cells. The prevalence of MGUS is 3.2% in persons ⩾50 years of age and 5.3% among persons ⩾70 years of age.[8] In a study of more than four million African-American and White veterans in the United States, the prevalence of MGUS in African-Americans was threefold higher than in Caucasians; however, the progression to MM at 10 years was virtually identical in both groups: 17% among African-Americans versus 15% among whites.[9] Patients with immunoglobulin (IgG) or IgA MGUS are at risk for progression to MM,

Table 3 Definitions of time to event end points

Endpoint[a]	*Definition*	*Comment*
TTP	Duration from start of treatment to disease progression, with deaths due to causes other than progression censored.	TTP is useful in assessing the activity of a drug and the durability of treatment benefit, but does not take into account the fact that a treatment may be associated with increased treatment related deaths and hence should be assessed in conjunction with progression free survival
PFS	Duration from start of the treatment to disease progression or death (regardless of cause of death), whichever comes first.	Should be reported in conjunction with TTP
EFS	The definition for EFS depends on how 'event' is defined. In many studies the definition of EFS used is the same as PFS. EFS may include additional 'events' that are considered to be of importance besides death and progression, including serious drug toxicity.	In general in myeloma, most studies reporting EFS are in fact referring to PFS. PFS is a more specific term and is the preferred term to be used, unless the definition of EFS includes additional 'events' besides progression or death that are considered important to take into account.
DFS	Duration from the start of CR to the time of relapse from CR. DFS applies only to patients in complete response.	Unlike TTP and PFS, the endpoint of DFS applies only to the subset of patients in complete response, and as such has limited value in myeloma at present.
DOR	Duration from first observation of partial response to the time of disease progression, with deaths due to causes other than progression censored. Duration of CR and PR should each be reported.	Unlike TTP and PFS, the endpoint of DOR applies only to a subset of patients in the study who achieve at least partial response. It expresses the durability of response.

Abbreviations: CR, complete response; DFS, disease-free survival; DOR, duration of response; EFS, event-free survival; PFS, progression-free survival; PR, partial response; TTP, time to progression.
[a]Time-to-event end points such as TTP, PFS and OS require a randomized comparative study to interpret the results.

primary amyloidosis or related disorders, while those with IgM MGUS may progress to Waldenstrom's macroglobulinemia or IgM lymphoma. In a study of 1384 individuals from 11 counties in Southeastern Minnesota from 1960 through 1994, the median age was 72 years. During follow-up, 115 persons developed a serious plasma cell disorder: 75 persons developed MM (a 25-fold relative risk), 19 persons developed immunoglobulin-M lymphoma (a 2.4-fold relative risk), 10 persons developed amyloidosis (an 8.4-fold relative risk) and 7 persons developed Waldenstrom's macroglobulinemia (a 46-fold relative risk). The relative risk of progression to these disorders was 7.3-fold greater than expected in a normal population. The cumulative probability of progression was 12% at 10 years, 25% at 20 years and 30% at 25 years, which is approximately 1% per year.[10] The initial concentration of serum M protein, type of M protein (IgA and IgM are at higher risk for progression), and the free light chain ratio are risk factors for progression. Patients with a combination of a serum M-protein level $\geqslant$1.5 g per 100 ml, IgA or IgM MGUS, and an abnormal serum-free light chain ratio had a risk of progression at 20 years of 58% compared to 5% when none of the risk factors were present.[11]

SMM is characterized by a serum M protein of $\geqslant$3 g per 100 ml and/or BM clonal plasma cells $\geqslant$10% and no end-organ damage. The risk of progression to symptomatic MM or amyloidosis was almost 10% per year for the first 5 years, 3% per year for the next 5 years, and then 1.2% per year for the following 10 years.[12] Patients with MGUS or SMM should be rechecked in 3–6 months to exclude emerging symptomatic MM. If stable, patients with MGUS should be re-evaluated at annual intervals, or perhaps less frequently if no risk factors are present.[11] Patients with SMM should be re-evaluated at 3- to 6-month intervals. No specific treatment is indicated to prevent progression of MGUS and SMM. Treatment should be deferred until end-organ damage occurs or is imminent, characterized by the presence of hypercalcemia, renal insufficiency, anemia or bone disease related to the plasma cell proliferative process.

Recommendations

The panel recommends improvement in OS as a clinically meaningful end point in trials in MGUS and SMM, along with little or no treatment-related toxicity. Although improvement in TTP or progression-free survival (PFS) may be additional end points, they are not recommended as primary end points at this time because the utility of TTP and PFS in predicting OS needs to be studied. Since previous studies have shown that early treatment of MM does not result in improvement in survival,[13,14] additional studies (such as fluorescence *in situ* hybridization or gene profiling) may identify patients at higher risk for progression who might benefit from earlier intervention. Progression of MGUS and SMM should be defined on the basis of development of end-organ damage, and not solely based upon an increase in M protein levels (Table 3). Since only a small number of patients with MGUS and SMM progress on a yearly basis, the number of subjects needed for a preventive strategy is large, even with refinements in prognostic criteria to select patients with higher risk.

In a population that may be at a low risk of progression, a most important issue is safety. Demonstration of a treatment capable of delaying progression requires a controlled clinical trial with a placebo comparator arm, which shows both improvement in OS and a low toxicity profile. Use of current agents outside the context of clinical trials is not recommended, given the uncertain potential benefit versus toxicity. The cost of performing fluorescence *in situ* hybridization or gene profiling to identify patients at high risk for disease progression must be balanced against the proportion of patients who might obtain benefit from this testing. At present, therefore, no current agents are recommended for clinical use in MGUS or SMM.

Newly diagnosed MM

The choice of treatment in newly diagnosed MM is typically predicated on eligibility for stem cell transplantation (SCT).[15]

High-dose therapy with autologous SCT is not curative in MM, but can prolong OS compared to conventional chemotherapy for some patients.[16,17] Newly diagnosed patients eligible for SCT receive induction therapy for approximately four cycles with a regimen such as thalidomide plus dexamethasone,[18,19] and then proceed to stem cell harvest, followed by either early or delayed transplant. Patients not eligible for SCT because of advanced age, poor performance status or comorbidities have traditionally been treated with melphalan plus prednisone (MP); recently the standard of care may have shifted to melphalan, prednisone and thalidomide (MPT) due to its reported survival benefit.[20] More recently, bortezomib[21,22] and lenalidomide[23] have also emerged as effective agents in the treatment of newly diagnosed MM. With the introduction of these new agents, the rates of complete response (CR), VGPR and partial response (PR) in previously untreated patients have improved dramatically.

For this group of patients, OS, TTP and PFS are appropriate end points in MM and can support drug registration when superiority can be demonstrated in randomized trials. However, in the setting of newly diagnosed MM, additional end points that clearly indicate clinical benefit need to be considered, since improvements in therapy have lengthened OS by a number of years. Furthermore, the number of salvage therapies available is constantly increasing and therefore likely will confound any meaningful analysis of OS for newly diagnosed patients. In addition, patients eligible for SCT, who are also typically the best candidates for clinical trials, commonly receive a fixed duration of induction therapy and then proceed to transplantation, making it difficult to evaluate the effect of pretransplant response status on long-term end points.

Recommendations

Although OS, TTP and PFS are the desirable clinical end points for newly diagnosed MM, CR rate and/or CR + VGPR rate are recommended as additional registration end points. In contrast, in newly diagnosed MM overall response (OR) (including PR or better) is not recommended as a meaningful end point alone.

CR now can be reliably defined and is an important goal of MM therapy[15,24] which can be reliably defined. Given that new therapies for previously untreated MM are producing OR rates in excess of 80–90%, it will be difficult to design trials to show superior OR as a primary end point alone. In contrast, CR rates, even with new regimens, are typically less than 30–40%. Evidence supporting CR as a clinically meaningful end point conveying a survival advantage includes: (1) an improvement in OS reported with high-dose therapy subsequent to improved CR in newly diagnosed MM;[16,17] (2) prolongation of event-free survival (EFS) and OS with melphalan–prednisone–thalidomide associated with improvement in CR rates;[20,25] (3) improved survival in newly diagnosed patients who achieve CR (using landmark analysis), with survival related to the quality of CR;[26] (4) achievement of CR associated with superior EFS and OS in a retrospective study of 344 MM patients treated with high-dose therapy and autologous SCT (ASCT);[27] (5) improved CR, EFS and OS duration with the earlier achievement of CR[28] and (6) correlation of CR with improved OS in MM.[29]

Although the IMWG response criteria[3] have identified a category of stringent CR, the consequences of achieving this level of response are as yet undefined. Additional molecular and immunophenotypic criteria[30] and improved imaging techniques, such as magnetic resonance imaging, should also be evaluated and incorporated. Patients not achieving CR are not necessarily a homogeneous group; some within this group may have survivals comparable to patients achieving CR. Finally, not all studies have found CR to be associated with improved survival,[31,32] and it is not known whether the quality of CR is different depending on prior therapy.

A strong consideration should also be given to a clinical end point of combined CR + VGPR, since patients with VGPR have had similar long-term outcome as those with CR. For example, in a randomized study of single versus double SCT, benefit of therapy was related to whether or not VGPR status was achieved after the first SCT,[33] that is, patients achieving VGPR or better did not benefit from a second transplant. In another study, the attainment of VGPR or better in newly diagnosed MM was one of the best predictors of OS.[34]

In contrast to achieving CR, the outcomes conveyed by achieving a PR or better (OR) are not well defined in the first-line setting. Prior studies in newly diagnosed MM have not shown prolonged OS associated with increased OR, although improvements were seen in EFS and PFS.[35] New therapies for previously untreated MM are associated with OR rates in excess of 80–90%, making it difficult to conduct randomized trials with superiority in OR as a regulatory end point.

Maintenance therapy

Maintenance is defined as 'the addition of therapy following completion of induction treatment in responding or non-progressing patients, with the goal of prolonging survival'. Although most patients now respond and CRs are becoming increasingly common following initial therapy for MM, most patients subsequently relapse. Thus, different maintenance strategies have emerged which attempt to prolong the duration of an initial or subsequent response. Early studies of maintenance therapy employing melphalan,[36,37] interferon[38–40] or corticosteroid[41,42] treatment often prolonged EFS, but not OS, and had substantial morbidity. Since ineffective maintenance strategies not only fail to benefit patients, but also bring additional cost, morbidity and reduced quality of life, these therapies are not routinely applied. Recently, however, studies have suggested an OS benefit for newer maintenance strategies, such as use of thalidomide after SCT.[43] Patient populations in whom maintenance therapies should be applied and suggested end points for subsequent drug approval were considered and reviewed.

Recommendations

In defining maintenance therapy, therapies applied throughout induction were not included, since the duration of conventional induction therapy is variable, and continuation of a therapy given from the onset of treatment would obscure the contribution of the maintenance phase to the regimen. For example, in Total Therapy 2, thalidomide was given throughout the study (induction, consolidation and maintenance). The reported benefit of thalidomide was an improved CR rate and a significantly longer 5-year EFS, but OS was not improved.[32] It is not possible from this study design to interpret the specific impact of the maintenance thalidomide. In relapsed patients responding to their salvage treatment, prolonging disease control is important; however, it is preferable to evaluate maintenance therapy in newly diagnosed patients where remissions are more likely to be durable and are not confounded by prior drug use. Transplant-eligible and transplant-ineligible patient populations should be separated, since therapy and end points are sufficiently different in these populations to require separate consideration.

The best end point for any evaluation of maintenance therapy is OS. Nevertheless, there are significant barriers to using OS as an end point in MM, including confounding subsequent therapy and the long duration of follow-up necessary to observe the end point. Also, patients who do not receive the investigational maintenance treatment in randomized trials may receive it later in the disease course. In these trials, the comparison is actually 'treatment X' as maintenance versus 'treatment X' at relapse, (that is, early versus delayed). The absence of a significant difference in the OS cannot simply be interpreted as a lack of efficacy of 'maintenance treatment X', since both groups could be benefiting from the drug.

Given the apparent impracticalities of OS as an end point, alternate end points as potential surrogates should be examined. EFS was considered as one such end point; however, many previous studies have shown prolonged EFS without improving OS, but with added costs and toxicity to patients; for example, use of interferon in numerous maintenance studies. Thus, EFS by itself has not been a particularly useful end point as a surrogate for OS. Completed and ongoing IFM trials of maintenance therapies have only shown benefit in patients who failed to achieve a CR with induction therapy, suggesting that the effectiveness of maintenance may be associated with the ability to obtain a CR. However, this data is preliminary, and in some studies improved CR rates have not translated into improved OS. Finally, the role of PRO was discussed, but the lack of validated tools and the quality of PRO data presently being obtained make this currently impractical. Thus, although neither EFS, CR or PROs alone were felt to provide the necessary burden of proof, a combination of these as appropriate end points may serve as a valuable surrogate for OS, that is, a trial which showed improved CR rates and EFS prolongation accompanied by improved (or at least not significantly diminished) quality of life would presumably be an advance for patients.

Given the importance but difficulty of evaluating OS in judging maintenance therapy, maintenance trials in high-risk patients could be considered. For example, after tandem transplant, low-risk patients may have a median OS of 7–8 years, while higher risk groups have a median OS of 4 years. Maintenance interventions might be testable in such subsets of patients in whom OS is not expected to be long so that an answer may be more rapidly forthcoming. Whether such interventions would be applicable to all risk groups would be a separate question.

Relapsed myeloma

Induction treatment for MM, particularly when followed by myeloablative therapy with stem cell support, results in at least PR for the majority of patients. Nearly all patients, however, eventually relapse and require additional therapy. Recently, bortezomib demonstrated an improvement in OR in a phase II clinical trial of patients with relapsing refractory MM (Summit), and a subsequent phase III trial (Apex) confirmed meaningful improvement in TTP and OS compared with dexamethasone alone.[44] Similarly, two phase III trials of lenalidomide–dexamethasone reported improved response, TTP, and OS versus dexamethasone-placebo.[45,46] These trials provided the basis for FDA approval of bortezomib (accelerated approval followed by full approval) and lenalidomide–dexamethasone for therapy of previously treated and relapsed MM.[44–46] These improvements in therapy, while welcome, present a new set of difficulties for future drug approval in the relapsed setting including: how best to define the relapsed population; how to incorporate cross-over designs which may confound differences in TTP and survival; and how new therapies can be tested against multiple active alternatives.

Recommendations

Three patient populations that have been included in studies of 'relapsed/refractory' MM include the relapsed but not refractory group, the primary refractory group, and the relapsed-and-refractory patient group. Historically, patients with relapsed disease have usually been distinguished from those in refractory relapse on the basis of sensitivity to vincristine–doxorubicin–dexamethasone.[47,48] The introduction of three novel agents and multiple new combinations of drugs with activity against relapsing MM make this historical definition obsolete. It is recommended that relapsing patients who are not known to be refractory be separated from those with primary refractory or relapsed-and-refractory disease. The duration of prior response or stable disease and the number and types of 'prior lines' of therapy may have differing impact and confer varying future sensitivity to therapy, depending on the agent to be evaluated. For instance, in the aforementioned phase III trials of bortezomib and lenalidomide–dexamethasone that demonstrated survival benefits in patients with relapsing MM, patients who had received oral melphalan–prednisone and patients who had received Total Therapy (induction therapy, tandem autologous stem cell transplant and maintenance therapy) were both considered to have had only one prior line of therapy, despite the fact that these significantly different prior exposures were likely to have introduced substantially different patterns of subsequent drug resistance.[25,32] Thus, relapsing MM should be defined as clinically active disease, not just biochemical M protein presence or increment, in patients who have received one or more prior therapies and with disease not refractory to the most recent treatment. 'Refractory to the prior treatment' means either (1) PD on last prior therapy; (2) best response of SD to last prior therapy or (3) PD within 3 months. Although this definition still includes a heterogeneous group of patients with varying degrees of disease stability and resistance based on various prior exposures and duration and quality of prior response, it does serve to separate relapsing patients from those with either newly diagnosed or refractory disease. For this relapsing group, a randomized-trial design, as described below, should balance the heterogeneity among these patients and allow treatment comparisons.

The clinical end points and types of trials appropriate for drug approval for patients with relapsing MM were reviewed. Prior to the approval of bortezomib and lenalidomide–dexamethasone therapy of previously treated MM, OR rates of 25–45% with combination therapy were usual for patients with relapsing MM. In the phase III trials of lenalidomide–dexamethasone, OR rates of more than 60% correlated with improved TTP and OS when compared with dexamethasone-placebo.[45,46] Similarly, treatment of patients with relapsing MM with single agent bortezomib, compared to single agent dexamethasone, resulted in a doubling of response that was associated with a near doubling of median TTP.[44] In these trials, improved OR correlated well with improved OS, although other trials have failed to demonstrate similar correlations.[31] Because of these inconsistencies and current alternative treatment options for this group of patients, it is suggested that clinical end points of TTP, PFS and OS, as demonstrated in randomized trials, are necessary for full drug approval in relapsing MM. There is a real concern that study designs incorporating automatic treatment crossover can obscure OS differences. Parallel companion trials are one

way of addressing this issue. It must be emphasized, however, that a drug would be of interest to relapsing patients, even if there was no overall benefit in TTP, PFS or OS, if a subgroup of patients with poor risk features (that is, cytogenetic chromosomal abnormalities, such as, deletion 13, t4;14, t14;16 prospectively defined) demonstrated a benefit in TTP or OS.[49] Additionally, other end points like time-to-event (TTE) markers were addressed. While these were not considered appropriate for general anti-MM chemotherapeutics for reasons previously discussed under PRO studies, it is suggested that for some studies of agents directed toward improving a specific clinical feature of MM, TTE parameters could be individualized and established. A good example is the prolonged median time to skeletal-related events in patients treated with bisphosphonates compared with placebo.[50]

Relapsed and refractory myeloma

Relapsed and refractory MM is a specific and unmet medical need, where median survival ranges from 6 to 9 months and responses to treatment are characteristically short.[51] Successive treatment regimens result in progressively lower response rates and decrease in duration of response, presumably secondary to increasing drug resistance[51] reflecting changes in disease biology, with more tumor cells expressing a more aggressive phenotype, higher proliferative thrust, and lower apoptotic rates. Although prognostic factors have been identified for newly diagnosed MM, factors that retain prognostic value in the context of relapsed and refractory disease remain to be defined. The advent of novel therapies targeting disease biology and tumor microenvironment has improved the outlook for patients with relapsed and refractory disease.[1,52] Bortezomib, thalidomide and lenalidomide now constitute 'backbone' agents in this setting.[44,53,54] Bortezomib in particular reflects a paradigm of drug development where accelerated FDA approval emerged from studies in this patient population, followed by full approval in the earlier patients with relapsed MM.[1,52] Patients with relapsed and refractory MM therefore remain an area of priority for clinical study, with the overall goal of improving survival.

Recommendations

OR and duration of disease control are appropriate end points for regulatory approval in this population. End points should include OR (CR plus PR plus MR, versus stable disease), but duration of benefit, as reflected by duration of response, PFS and OS, is vital.[31,55] Toxicity, quality of life and PROs are important, but in heavily pretreated refractory patients are difficult to use comparatively. The binary outcome of survival (versus not) is a primary goal, although treatment–emergent toxicities also require careful attention.

Although the modified EBMT criteria have been the benchmark for assessing response, the proposed IMWG should be integrated since they provide improvements in assessing CR, confirm durability and better define disease progression.[3,4,56] The roles for light chain quantitation and VGPR versus near CR (defined as CR with immunofixation positivity only) status require validation. It is suggested that MR remain a reportable response category, especially as this is associated with clinical benefit in this population.[5]

An important issue for studies in this population is the number and type of prior therapies which define the refractory state: refractoriness to two or more previous regimens is suggested for enrollment in Phase I trials, recognizing that assessing toxicity is a primary end point. For phase 2 trials, patients should be stratified by having received 2 versus 3 or more previous regimens, with prior treatments including other approved agents (for example, lenalidomide, thalidomide and/or bortezomib). It should also be recognized that this is an enriched population for new targets and biologic correlates. Moreover, complete and stringently collected data are vital to the assessment of any end point.

Relapsed-and-refractory MM is defined as relapse of disease in patients who must have achieved MR or better, which either becomes non-responsive while on salvage therapy, or progresses within 60 days of last therapy.[6,52] Characteristically, they have a poor prognosis; that is, median OS of 6–9 months, especially with ineffective therapy.[51] Refractory disease includes patients who never achieve MR or better: it includes 'non-responding but non-progressing' patients, in whom there is no significant change in M protein and no evidence of clinical progression; and 'primary refractory, progressive disease.' Distinguishing drug-resistant disease from inadequate therapy because of treatment intolerance, while an interesting clinical question, amounts to the same clinical outcome (that is, treatment failure).

New therapies for patients with relapsed and refractory disease should be considered for the accelerated approval pathway.[52] Response rates, especially high-quality responses of substantial duration are important indicators of benefit. Such patients may have extramedullary disease, the evolution of hyposecretory MM (which is relevant for the use of free light chain assessment), advanced bone disease, low platelet counts, renal failure and low-serum albumin. While CR and PR should be adopted as a benchmark in this setting, other lesser degrees of response are informative. For example, MR may be important, especially if long lasting (for example, 3–6 months) and associated with documented symptomatic benefit. Thus, key end points in such patients include duration of response, PFS and OS.[31,55] Improvements in PROs are important clinically, but the challenges of obtaining these measurements in sick patients with advanced disease are daunting at present.

The lessons learned from bortezomib and lenalidomide in the relapsed and refractory populations are instructive.[6,44,54] For bortezomib, rapid accrual to clinical trials with significant response (CR + PR), durable response (as reflected by TTP), and PFS and OS as end points for accelerated approval were achieved. In the SUMMIT trial, the CR + PR rate with bortezomib monotherapy was 28%, the median duration of response was 13 months, and the median OS was 17 months.[6] Moreover, 19 (10%) patients exhibited either CR or near CR, and 12 of 19 achieved their first ever CR. The Phase II CREST study, which showed similar response rates, provided supportive data for the SUMMIT results.[3,56] A multicenter, single-arm, open-label phase study of 220 patients at 30 sites (the 014 phase II clinical trial) evaluated single-agent lenalidomide in relapsed and refractory MM.[54] End points included RR (using modified EBMT criteria) and TTP. Patients were treated who had stable disease before progression on prior therapy; PD despite salvage anti-MM therapy; and documented evidence of disease progression during the last prior therapy of at least two cycles. Patients may have been previously treated with thalidomide, bortezomib or both. The OR was 27% and the median TTP was 22.4 weeks (range = 1–92 weeks).[54] Thus, despite modest OR, the durability of benefit in responding patients was noteworthy.

Conclusions

At present MM can be considered as a group of disease states, somewhat arbitrarily subdivided based on current treatment

options and varying biologic behavior. New treatments may alter the present conceptual framework through the achievement of ever higher quality responses of increasing durability and safety. Convincing demonstrations of improvements in treatment effect require comparative study designs using well-defined, explicit end points analyzed in well-defined patient groups. Scientific advances in MM hold great promise to improve patient outcome in the future.

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Appendix

ASH/FDA Panel on Clinical Endpoints in Multiple Myeloma

Workshop Co-Chairs

Kenneth C Anderson, MD, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.

Richard Pazdur, MD, US Food and Drug Administration, Silver Spring, Maryland, USA.

American Society of Hematology Liason

James N George, MD, University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, USA.

Monoclonal Gammopathy of Undetermined Significance/Smoldering Multiple Myeloma Subcommittee.

Chair: Robert A Kyle, MD, Mayo Clinic, Rochester, Minnesota, USA.

Geraldine P Schecter, MD, Veterans Affairs Medical Center Washington, Washington, DC, USA.

Ann T Farrell, MD, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.

Rafael Fonseca, MD, Mayo Clinic, Scottsdale, Arizona, USA.

Newly Diagnosed Multiple Myeloma Subcommittee

Chair: S Vincent Rajkumar, MD, Mayo Clinic, Rochester, Minnesota, USA.

Bart Barlogie, MD, PhD, University of Arkansas for Medical Science, Little Rock, Arkansas, USA.

Sundar Jagannath, St Vincents Hospital, New York, NY, USA.

Kaushikkumar Shastri, MD, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.

Jesus F San Miguel, MD, PhD University of Salamanca, Salamanca, Spain.

Mario Boccadoro, University of Torino, Torino, Italy.

Maintenance Subcommittee

Chair: Keith Stewart, MD, Mayo Clinic, Scottsdale, Arizona, USA.

Peter F Bross, MD, Center for Biologics Evaluation and Research, US Food and Drug Administration, Rockville, Maryland, USA.

Nikhil C Munshi, MD, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.

Jean-Luc Harousseau, University of Nantes, Nantes, France.

Relapsed Multiple Myeloma Subcommittee

Chair: Donna Weber, MD, MD Anderson Cancer Center, Houston, Texas, USA.

Brian Durie, MD, Cedars Sinai Medical Center, Los Angeles, California, USA.

Vicki L Goodman, MD, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.

Sagar Lonial, MD, Emory University, Atlanta, Georgia, USA.

Robert Z Orlowski, MD, PhD, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

Melissa Alsina, H Lee Moffitt Cancer Center, Tampa, Florida, USA.

Relapsed Refractory Multiple Myeloma Subcommittee

Chair: Paul G Richardson, MD, Dana-Farber Cancer Institute, Boston, Massachusetts, USA.

Joan Blade, MD, Hospital Clinic of Barcelona, Barcelona, Spain.

Donna Reese, MD, Princess Margaret Hospital, Toronto, Ontario, Canada.

William Dalton, MD, H Lee Moffitt Cancer Center, Tampa, Florida, USA.

Seema Singhal, MD, Lurie Cancer Center, Northwestern University, Chicago, Illinois, USA.

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Mohamad Hussein, MD, Cleveland Clinic, Cleveland, Ohio, USA.

US Food and Drug Administration Representative

Robert Kane, MD, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.

Industry Representative

Robert J De Lapp, MD, PhD, Celgene Corporation, Summit, New Jersey, USA.

National Institutes of Health Representative

Donna Griebel, MD, Division of Cancer Prevention, National Cancer Institute, Rockville, Maryland, USA.

Patient Representatives

Bruce Holmberg, Rockville, Maryland, USA.

James L Omel, MD, Grand Island, Nebraska, USA.

Statisticians:

John D Crowley, PhD, Southwest Oncology Group Statistical Center, Seattle, Washington, USA.

Rajeshwari Sridhara, PhD, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.

Representatives from Advocacy Groups

Anne Quinn Young, MPH, Director of Programming, Multiple Myeloma Research Foundation.

Brian Durie, MD, Chair, Board of Directors, International Myeloma Foundation.