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Persistent challenges with treating multiple myeloma early

Aaron M. Goodman,[1] Myung S. Kim,[2] and Vinay Prasad[3,4]

[1]Division of Blood and Marrow Transplantation, Department of Medicine, University of California, San Diego, La Jolla, CA; [2]Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR; and [3]Department of Medicine and [4]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA

Over the past decade, 2 strategies have advanced the treatment of patients with multiple myeloma and its precursor diseases. First, the definition has changed to include patients without end organ damage, who previously would not have been treated. Second, there is widespread enthusiasm for treating high-risk, smoldering multiple myeloma. In this commentary, we explore the evidence supporting these therapeutic expansions. Although early treatment adds cost and therapeutic burden, it remains unknown whether survival and health-related quality of life are improved by early treatment. Herein, we consider the implications of diagnostic expansion in multiple myeloma. (*Blood*. 2021;137(4):456-458)

Historically, multiple myeloma has been diagnosed based on end organ damage. To have multiple myeloma, a plasma cell's proliferation and its antibody production had to have damaged a patient's bones, blood cell production, or kidneys. End organ damage also marked the onset of treatment.

In recent years, this criterion has changed. There is now enthusiasm about treating smoldering multiple myeloma (SMM), a precursor disease state, and about changing the definition of multiple myeloma to include disease states that were previously considered precursors. Both of these actions result in administration of drugs to patients who historically have not been treated. Because multiple myeloma is incurable, the patient will continue to take these drugs for life.

Treating early may be the best approach, if, in fact, it results in improved survival or health-related quality of life (HRQoL) over treatment at the point of end organ damage. Alternatively, it may be problematic if early treatment results merely in more years of exposure to drug therapy without countervailing benefit. In this commentary, we explore the evidence base for this change in practice. Will moving the starting point of treatment of myeloma and its precursor states yield robust results?

Broadening the definition of myeloma

In 2014, the International Myeloma Working Group changed multiple myeloma's definition to include 3 new diagnostic criteria: the presence of >60% bone marrow plasma cells, the presence of bone lesions on magnetic resonance imaging, and a free light chain (FLC) ratio >100.[1] These diagnostic criteria expanded multiple myeloma beyond end organ damage to a disease that now includes patients who, by definition, have no end organ damage and are asymptomatic.

Consider the skewed FLC ratio. The paper cited in support of this approach was published in 2013 by Larson and colleagues from the Mayo group.[2] In this study, 586 patients with SMM were studied to determine the threshold at which the FLC ratio is associated with an 80% probability of progression to multiple myeloma or a related plasma cell dyscrasia at 2 years. For patients with an FLC ratio of at least 100 (n = 90) the risk of progressing to multiple myeloma or amyloid light-chain amyloidosis was 79% at 2 years.

One of the key points is that patients with FLC ratios >100 did not universally or rapidly progress to multiple myeloma. A skewed FLC does not guarantee progression. In fact, at 3-year follow-up, 10% of patients still had not progressed to multiple myeloma. In contrast to the Mayo findings, Waxman and colleagues from the University of Pennsylvania found a lower rate of progression at 2 years (64%) in patients with an FLC ratio of at least 100.[3] The Greek Myeloma Study Group reported that nearly all patients with an FLC ratio of at least 100 progressed to multiple myeloma; however, this study included only 7 patients with an FLC ratio >100.[4]

Using a serum FLC ratio of at least 100 as the sole criterion for treating active multiple myeloma guarantees that some patients who would not progress in the next 3 years will receive multidrug myeloma treatment. This approach would add therapeutic burden and cost to their myeloma precursor diagnosis, but, by definition, would not make them feel better. Whether this treatment is associated with increased longevity is unknown, as no randomized trials of early vs delayed treatment have been conducted to test this diagnostic criterion.

Randomized trials of treating SMM leave open questions

There has been heightened interest in treating high-risk SMM in recent years. SMM can be stratified into groups, depending on the risk of progressing to multiple myeloma. The most widely used model is the 2018 Mayo Clinic model (20-2-20 criteria). This

risk stratification model takes into account the following 3 criteria: bone marrow plasma cell percentage >20%, M-protein >2 g per day, and ratio of involved to uninvolved FLC >20%. Low, intermediate, and high risk is defined as meeting 0, 1, and 2-3 of the criteria, respectively, with a 2-year risk of progression to myeloma of 6%, 32%, and 69%.[5] The PETHEMA (Malignant Hematology Treatment Program) model uses the proportion of aberrant bone marrow plasma cells within the bone marrow plasma cell compartment of ≥95% on flow cytometry and reduction of uninvolved immunoglobulins (immunoparesis). With 0, 1, or 2 risk factors, the 5-year progression-free survival is 72%, 46%, and 4%.[6] The PETHEMA criteria are based on testing that is not widely available. Interestingly, the 2 risk models show significant discordance, with many high-risk patients in one model being low risk in the other model.[7] These risk models are incomplete, as evidenced by the discordance between the 2 models, and do not perfectly predict patients who will progress to myeloma, inevitably leading to intensive treatment of patients in whom disease would not have progressed.

Randomized, controlled trials of treatment of high-risk SMM have left us with unresolved questions. A 2013 study by Mateos and colleagues in *The New England Journal of Medicine* has 2 limitations.[8] First, the control arm (patients with high-risk SMM by the PETHEMA criteria who were under observation) had some patients who eventually developed myeloma that required treatment. The trial unfortunately did not use the prevailing standard of care in the United States at the time, and thus, the trial assessed lenalidomide (Revlimid) and dexamethasone for SMM vs substandard care upon progression. Second, the trial was a phase 2 trial that was underpowered for determining overall survival (OS). When a trial lacks power, positive results are often exaggerated and may even be false positives.[9]

Recently, in cancer medicine, we saw how underpowered phase 2 trials can mislead. The use of olaratumab for soft tissue sarcoma received US Food and Drug Administration accelerated approval based on a small phase 2 trial that found a large survival benefit, but when the drug was reassessed in a phase 3 confirmatory trial, the results were entirely null. Olaratumab offered no benefit and was withdrawn from the market.[10] In other words, although Mateos et al[8] showed a large survival benefit in treating SMM, their study was not powered for OS, and thus the survival results from that study are unreliable.

A confirmatory study of lenalidomide in SMM was launched by the Southwest Oncology Group. This study found a progression-free survival benefit, but had not demonstrated a survival benefit when the investigators decided to cross all patients to the investigational agent.[11] This protocol change unfortunately precluded the trial from providing a reliable answer on whether early treatment is superior to delayed treatment, as patients in both arms have now been treated earlier than they would be with the use of standard care.

Moreover, a subsequent randomized trial no longer uses observation as the control arm and is using lenalidomide and dexamethasone as the control arm in current enrollees (www.clinicaltrials.com #NCT03937635). Thus, whether early treatment of SMM improves OS will forever be an unanswered question.

Uncontrolled studies of SMM

In addition to randomized trials in SMM, there are ongoing uncontrolled studies with results that will be impossible to interpret because they lack a control arm. Specifically, trials are under way of multidrug combinations and high-dose chemotherapy followed by autologous stem cell transplantation for SMM. The Black Swan Research Initiative, sponsored by the International Myeloma Foundation, is currently running the ASCENT (Aggressive Smoldering Cure Evaluating Novel Therapies) and GEM-CESAR (Curative Strategy) trials based in the United States and Europe, respectively.[12] The GEM-CESAR protocol entails giving asymptomatic patients six 4-week cycles of carlfizomib/lenalidomide/dexamethasone, followed by high-dose melphalan autologous stem cell transplantation, intensification with 2 chemotherapy consolidation cycles, and maintenance with lenalidomide and dexamethasone for up to 2 years.[13] Because this trial has no control arm, the question of whether early treatment of SMM will result in improved OS or a cure will not be answered by this or other similar protocols. Drugs that are active in myeloma will undoubtedly be active in precursor plasma cell states where patients can only be younger and healthier; however, knowing that these drugs are active provides no information as to whether we ought to treat such patients. The relevant question of whether it is better to treat early or later cannot be answered by an uncontrolled study. Preliminary results of GEM-CESAR were presented at the American Society of Hematology Conference in 2019. As expected, significant toxicity, including 2 deaths, was reported. Whether the protocol used in this trial hastens death or extends life is unknown.

Conclusion

The rationale for broadening the disease definition of myeloma and the treatment of SMM is to identify patients early in the course of the disease who benefit from treatment by improving quality of life and survival. Unfortunately, current data have not tested the relevant question. Would a randomized trial, designed and powered for OS or HRQoL, show that early treatment is better? We already know treatment of symptomatic patients with immunomodulators, proteasome inhibitors, and high-dose chemotherapy is safe and effective. Single-arm studies proving the safety and efficacy of these drugs in asymptomatic individuals answer an obvious question. Of course, drugs that can be given later to a patient can be given sooner. But is early treatment valuable?

Treatment of multiple myeloma is expensive (>$200 000 US for 1 year of lenalidomide), and introducing these agents earlier in the disease course would result in a great cost to society and an increased therapeutic burden. Without knowledge of improvement in OS and/or HRQoL, we cannot justify treating asymptomatic patients with expensive and toxic drugs, particularly when some patients are not destined to progress to symptomatic disease. We fear that treating SMM will soon become the norm, even though we will not have answered the most fundamental question: whether treating precursor myeloma disease states benefits patients.

Authorship

Contribution: A.M.G., V.P., and M.S.K. designed the paper, constructed the arguments, and wrote the paper.

Conflict-of-interest disclosure: V.P. has received research funding from Arnold Ventures, royalties from Johns Hopkins Press and Medscape; honoraria for grand rounds and lectures from universities, medical centers, nonprofit organizations, and professional societies; consulting fees from UnitedHealthcare and New Century Health; speaking fees from Evicore; and remuneration for a Plenary Session podcast that has Patreon backers. A.M.G. is a consultant for EUSA Pharma and Seattle Genetics. M.S.K. declares no competing financial interests.

ORCID profiles: M.S.K., 0000-0002-2042-1262; V.P., 0000-0002-6110-8221.

Correspondence: Vinay Prasad, University of California, San Francisco, 550 16th St, San Francisco, CA 94158; e-mail: vinayak.prasad@ucsf.edu.

Footnote

Submitted 1 November 2020; accepted 18 November 2020; prepublished online on *Blood* First Edition 24 November 2020. DOI 10.1182/blood.2020009752.

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