Smoldering multiple myeloma: special considerations surrounding treatment on *versus* off clinical trials

Elisabet E Manasanch,[1] Neha Korde,[2] Sham Mailankody,[3] Nishant Tageja,[3] Manisha Bhutani,[3] Mark Roschewski,[3] and Ola Landgren[2]

[1]Department of Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX; [2]Myeloma Service, Memorial Sloan-Kettering Cancer Center, New York, NY; [3]Multiple Myeloma Section, Lymphoid Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, USA.

E-mail: EEManasanch@mdanderson.org or landgrec@mskcc.org *doi:10.3324/haematol.2014.107516*

Over the past decade, treatment outcomes for multiple myeloma (MM) patients have improved and it has become increasingly clear that deeper responses correlate with better outcomes.[1-4] Emerging data suggest that early treatment can achieve deep responses.[5] A recent randomized phase III clinical trial reported a prolongation in progression-free survival (PFS) and overall survival (OS) with early treatment of patients with high-risk smoldering multiple myeloma (SMM).[6] Typically, these patients are diagnosed incidentally on routine evaluations and have no end-organ damage.[7] Given that a key aspect of clinical medicine is "first, do no harm", a dilemma exists regarding early intervention for SMM.

Clinical trials in medicine are systematic investigations to develop generalizable knowledge. In the field of multiple myeloma, unanswered fundamental questions need to be addressed through clinical trials. Is earlier treatment in myeloma adequate? When should treatment be initiated? What population is the most likely to benefit? What treatment strategy should we use? What type of disease monitoring after initial therapy should we employ?

A fundamental challenge is how to answer these questions while simultaneously preserving the core principles of the Belmont Report, including: 1) respect; 2) beneficence; and 3) justice for patients seeking treatment on trials. The Belmont Report was published by the US Department of Health, Education and Welfare in 1979 as a statement of basic principles and guidelines with regard to research in humans.[8]

Respect refers to the fact that research participants should be treated as autonomous agents and persons with diminished autonomy should be protected from research that they may not fully understand in order to prevent coercion. This assumes that patients participate in trials on a voluntary basis and are provided with adequate information to make an informed decision. Before enrollment in an SMM treatment trial, patients should be aware that the "watchful waiting" approach remains a legitimate strategy given the body of current evidence. It is important to note that there is significant discordance (>70%) in the overall SMM patient risk classification and that prospectively obtained risk models are not yet widely in use[9,10] Thus, better predictive models and biomarkers need to be validated prospectively before one can determine an individual's lifetime risk of disease progression with certainty. Despite recent advances, the standard of care of SMM remains a "watchful waiting" approach, as larger international randomized studies and longer follow up are awaited.

The current lack of individualized tools poses a dilemma when determining the best treatment approach for SMM patients. Given that patients with precursor disease do not universally develop malignancy, and that among those who transform from SMM to MM the time window varies greatly, treatment toxicity remains a concern. Although contemporary anti-myeloma therapies are better tolerated now than in the past, serious toxicities may ensue. Thus, it is mandatory to carefully consider the risks/benefits for each patient before enrollment in a treatment trial for SMM.

Beneficence refers to the need "not to harm" the patient and to "maximize benefits and minimize possible harms". The critical question is whether the benefits of treatment of SMM are justifiable in the light of the risks involved. End-organ damage poses a serious threat to patient health; good clinical practice would mandate for treatment intervention if it were certain that this would develop. In fact, monoclonal gammopathy of undetermined significance (MGUS) and SMM precede MM in every case, and this poses an opportunity for early intervention and prevention.[11,12] A recent trial has shown that early intervention delays end-organ damage and can alter the course of the disease.[6] As extrapolated from other medical conditions, including other solid and hematologic malignancies, one may conjecture that early intervention has the potential to provide a path to a cure in myeloma. Alternatively, one may speculate that early intervention may result in better control of the disease, reflected in a need for chronic/extended therapy paired with longitudinal minimal residual disease monitoring.[13] These hypotheses need to be formally tested in future clinical investigations.

The third principle of the Belmont report refers to the value of justice as a "fairness of distribution" of the risks/benefits derived from research. In the past, research subjects tended to be poor patients or people of certain races or ethnicities, who were often not informed of their participation in clinical trials and may have been coerced to participate. Thus, these patients were prone to receive most of the harm from research whereas private patients received the benefits of improved medical care. SMM treatment protocols should include patients from all socio-economic backgrounds and racial ethnicities who are likely to benefit the most from subsequent research applications.

Another important challenge for SMM treatment includes outcome measures in clinical trials. Traditionally, clinical outcomes in medicine have involved PFS and OS. Lately, surrogate end points have accounted for approximately 20% of new drug approvals by the US Food and Drug Administration (FDA).[14] In addition to more traditional end points, delayed progression to MM, prevention of disease complications, or evidence of minimal residual disease should be explored as surrogate end points in patients with SMM.

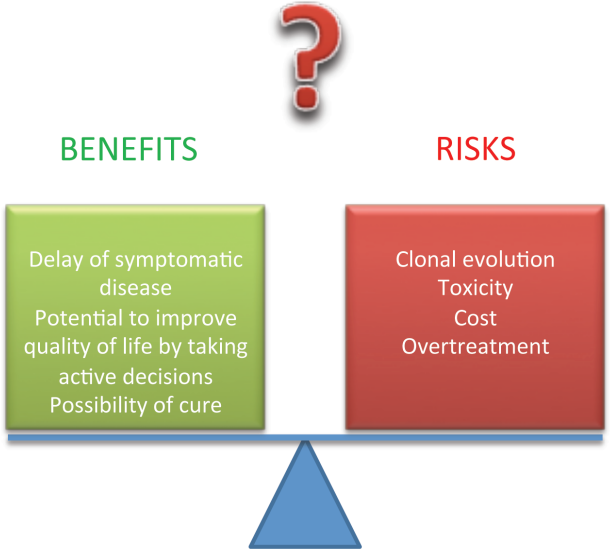
Potential long-term harms resulting from SMM treatment should be openly discussed with patients before enrollment in a clinical trial. In recently published molecular and genetic studies, MM was composed of massive genetic heterogeneity with-

in a given patient. Indeed, at MM diagnosis, recent data inform us that there is no single clonal population of malignant plasma cells but rather different subpopulations that are branching off an original clone.[15,16] Although the dynamics of these subpopulations still have to be better defined both in the presence and absence of anti-myeloma therapy, based on theoretical models, it has been proposed that they are competing for survival in the tumor microenvironment. At earlier stages of disease (i.e. at SMM), one might speculate that lower disease burden and/or fewer molecular subpopulations of abnormal plasma cells may result in higher susceptibility to therapy. On the other hand, one may speculate that early treatment could eradicate subpopulations of abnormal plasma cells while one or a few "non-treatment susceptible populations" remain viable and can grow alone without competing treatment susceptible clones. At this time, we do not know which of these statements is right and this is subject to speculation. In order to address this fundamental question, we need well-designed translational clinical studies focusing on early intervention. This may also allow for a better distinction between low-risk SMM, which may be less likely to benefit from therapy, and early myeloma, where intervention might change the course of the disease. Taken together, it is unknown whether early treatment will lead to selection of more resistant myeloma cells, or, if it might have the potential to facilitate the framework for a cure for myeloma, at least in some patients. Prospective studies are required to address these key questions.

Should we consider SMM treatment outside of clinical trials? Currently, the standard of care of SMM patients is observation for the development of symptomatic MM and to reserve treatment for development of end-organ damage. Based on institutional retrospective studies derived from small numbers of patients, the Mayo Clinic group has proposed a new definition of MM based on extensive bone marrow infiltration by plasma cells (≥60%) and highly skewed serum free light chain ratio (sFLC≥100) that would require treatment before end-organ damage ensues.[17] Importantly, due to inherent problems related to the small number of cases, until we have access to prospective data, collaborative efforts are needed to better characterize these features. Future investigations based on larger numbers of patients collected from prospective studies will provide more robust answers and help clarify these issues.

The improved toxicity profiles and clinical outcomes of newer medications have compelled many patients with smoldering disease to consider treatment in clinical trials. Some of these patients, however, may not be eligible for a particular trial due to overly restrictive inclusion criteria, financial concerns or the inability to travel to large specialized centers that may be conducting such trials. In these situations, patients and their physicians may consider therapy for SMM. A major concern of treatment outside of clinical trials might be the cost of novel anti-myeloma therapies, which are amongst the most expensive medications on the market. For example, both lenalidomide and carfilzomib cost around 10,000 USD/month and are not approved as an indication for treatment of SMM, making reimbursement by third-party payers practically impossible.[18,19] Significant side effects, including deep venous thrombosis/embolism, cardiac failure and neuropathy, are an important concern when debating whether to treat patients with SMM outside of clinical trials. This leaves the patient and the physician to wonder if there are sufficient data to support treatment outside of clinical trials. Should we then wait to have scientific evidence from larger, better-designed prospective studies to treat earlier? Or, should physicians make decisions regarding treatment of SMM based on their own clinical experience, even if numbers of patients are small? In the absence of data, similar to other clinical scenarios, probably, both doctrines, empiricism and rationalism, should co-exist and be utilized in the diagnosis and treatment of individual patients as fundamental questions about SMM remain unanswered.[20]

In summary, treatment of SMM is a complex matter. It requires extensive discussion and understanding of the risk and benefit ratio for each individual patient (Figure 1). Well-designed translational clinical trials are urgently needed to answer these important questions.



As we develop therapies that have lower toxicities and have increasingly higher efficacy for the disease in which they are intended, including the possibility of cure, the number of patients willing to undergo such treatments will also increase. In SMM, clinicians need to discuss the risks and benefits with patients and stay up-dated as more data become available. Until we have access to better knowledge, in circumstances where the benefit of early treatment in terms of overall survival is not well established, greater caution should be exercised in considering the risks versus *benefits of treatment.*

Figure 1. The fine balance in the benefit to risk ratio of treatment in patients with smoldering multiple myeloma.

Ola Landgren is the Head of the Myeloma Service at the Memorial Sloan-Kettering Cancer Center, New York, USA. His main fields of interest are multiple myeloma, smoldering multiple myeloma, MGUS, and related plasma cell disorders. Elisabet E. Manasanch is Assistant Professor at the Department of Lymphoma/Myeloma, Division of Cancer Medicine at the University of Texas, MD Anderson Cancer Center, USA. Her main fields of interest are multiple myeloma and related plasma cell disorders. Neha Korde is an attending physician at the Myeloma Service at the Memorial Sloan Kettering, NY, USA. Her main field of interest is plasma cell disorders. Sham Mailankody is a clinical fellow at the Myeloma Service at the National Institutes of Health, Bethesda, MD, USA. Her main field of interest is plasma cell dis-

orders. Nishant Tageja is a clinical fellow at the Myeloma Service at the National Institutes of Health, Bethesda, MD, USA. His main field of interest is plasma cell disorders. Manisha Bhutani is a clinical fellow at the Myeloma Service at the National Institutes of Health, Bethesda, MD, USA. Her main field of interest is plasma cell disorders. Mark Roschewski is a staff clinician at the Myeloma Service at the National Institutes of Health, Bethesda, MD, USA. His main fields of interest are lymphoma and plasma cell disorders.

Financial and other disclosures provided by the author using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are available with the full text of this paper at www.haematologica.org.

References

1. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. J Clin Oncol. 2010;28(5):830-4.
2. van de Velde HJ, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Haematologica. 2007;92(10):1399-406.
3. Paiva B, Vidriales MB, Cervero J, Mateo G, Perez JJ, Montalban MA, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood. 2008;112(10):4017-23.
4. Kapoor P, Kumar SK, Dispenzieri A, Lacy MQ, Buadi F, Dingli D, et al. Importance of achieving stringent complete response after autologous stem-cell transplantation in multiple myeloma. J Clin Oncol. 2013;31(36):4529-35.
5. Landgren O, Mailankody S, Kwok M, Manasanch E. Clinical and correlative pilot study of carfilzomib, lenalidomide and dexamethasone followed by lenalidomide extended dosing (CRd-R) in high risk smoldering multiple myeloma patients. Blood. 2013;122:1939.
6. Mateos MV, Hernandez MT, Giraldo P, de la Rubia J, de Arriba F, Lopez Corral L, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med. 2013;369(5):438-47.
7. Landgren O. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: biological insights and early treatment strategies. Hematology Am Soc Hematol Educ Program. 2013;2013:478-87.
8. The Belmont Report. Available from: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html
9. Cherry BM, Korde N, Kwok M, Manasanch EE, Bhutani M, Mulquin M, et al. Modeling progression risk for smoldering multiple myeloma: results from a prospective clinical study. Leuk Lymphoma. 2013;54(10):2215-8.
10. Dhodapkar MV, Sexton R, Waheed S, Usmani S, Papanikolaou X, Nair B, et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). Blood. 2014;123(1):78-85.
11. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009;113(22):5412-7.
12. Weiss BM, Abadie J, Verma P, Howard RS, Kuehl WM. A monoclonal gammopathy precedes multiple myeloma in most patients. Blood. 2009;113(22):5418-22.
13. Roschewski M, Korde N, Wu SP, Landgren O. Pursuing the curative blueprint for early myeloma. Blood. 2013;122(4):486-90.
14. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. JAMA. 2014;311(4):368-77.
15. Egan JB, Shi CX, Tembe W, Christoforides A, Kurdoglu A, Sinari S, et al. Whole-genome sequencing of multiple myeloma from diagnosis to plasma cell leukemia reveals genomic initiating events, evolution, and clonal tides. Blood. 2012;120(5):1060-6.
16. Lohr JG, Stojanov P, Carter SL, Cruz-Gordillo P, Lawrence MS, Auclair D, et al. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. Cancer Cell. 2014;25(1):91-101.
17. Dispenzieri A, Stewart AK, Chanan-Khan A, Rajkumar SV, Kyle RA, Fonseca R, et al. Smoldering multiple myeloma requiring treatment: time for a new definition? Blood. 2013;122(26):4172-81.
18. Medicaid Claims October-December 2013. Available from: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=6&ved=0CFQQFjAF&url=http%3A%2F%2Fwww.fdhc.state.fl.us%2Fmedicaid%2Fprescribed_drug%2Fxls%2F2013Q4_Report_01-23-14.xls&ei=QOD_UufIGIeX0QHkrYCgBQ&usg=AFQjCNEXFgkqx2J_uRra6IeAewD8lvWvew&bvm=bv.61535280,d.dmQ
19. Kyprolis product fact sheet, 2014. Available from: http://www.kyprolis.com/Areas/Hcp/content/pdfs/KYPROLIS%20Product%20Fact%20Sheet.pdf
20. Prasad V. Regarding empiricism and rationalism in medicine and 2 medical worldviews. Mayo Clin Proc. 2014;89(1):137.