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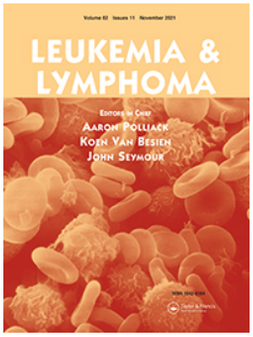

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LETTER TO THE EDITOR

The landscape of trials for smoldering multiple myeloma: endpoints, trial design, and lessons learnt

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Smoldering multiple myeloma (SMM) is a precursor disease state to multiple myeloma (MM) historically defined as meeting serological or morphological parameters of MM but with no evidence of end-organ damage. The definition of what constitutes MM versus SMM changed in 2014 to include presence of $\geq$60% bone marrow plasma cells, bone lesions on advanced imaging, and a free light chain (FLC) ratio $\geq$100 even in the absence of any other evidence of end-organ dysfunction [1].

High risk SMM has been defined differently by various groups [2, 3], but all of these risk models have a high risk of progressing to MM within 2 years. However, in all models, there are some patients that do not progress. Furthermore, significant discordance exists between these risk models [4]. Yet, recent guidelines recommend treating SMM even outside the context of a clinical trial [5] based on improvements in progression free but not overall survival.

The objective of our report was to determine the landscape of clinical trials enrolling patients with SMM by assessing the design of the studies, the interventions used, and the endpoints being assessed.

A search on clinicaltrials.gov was performed on 1 February 2021 using keywords, 'smoldering multiple myeloma,' 'smoldering plasma cell myeloma,' and 'smoldering myeloma.' A concurrent search was conducted on eudract.ema.europa.eu was also performed. We included all interventional studies that enrolled from 1 January 2011 to 31 January 2021. We included all active and completed studies regardless of their enrollment status (listed but not yet enrolling, active enrollment, suspended enrollment, and completed enrollment were all included). We excluded trials that were terminated without subject enrollment.

After excluding duplicates between the two databases as well as non-interventional studies such as registry studies, a total of 32 studies were identified. Table 1 lists characteristics of these studies.

The total number of patients projected to enroll/actually enrolled on these 32 studies were 2764, out of which 1817 patients (65.7%) were enrolled/projected to enroll in randomized studies and 947 in non-randomized studies. The most commonly used primary endpoints were response-based endpoints (13/32, 40.6%) and progression free survival (10/32, 31.2%). Only one study (3.1%) had a primary endpoint of overall survival and quality of life. The majority of studies (23/32, 71.9%) were assessing regimens or drugs with established safety and efficacy in MM. Fourteen trials (43.8%) were assessing regimens already established in MM in a non-randomized uncontrolled fashion with an endpoint of either response rate or progression-free survival.

We demonstrate that the majority of trials for SMM are non-randomized and have surrogate endpoints as the primary endpoint. There has been only one trial designed in the last 10 years with overall survival and quality of life as a primary endpoint (NCT03937635). Almost half the trials that have enrolled or are enrolling currently for SMM, are assessing regimens already established in MM in a non-randomized uncontrolled fashion with an endpoint of either response rate or progression-free survival. Due to the absence of control arms, these trials do not answer whether early treatment of SMM will result in improvement in overall survival or quality of life compared to current standard of care treatment upon progression [6]. It is intuitive that drugs that are active in MM will be active in precursor states where patients are healthier.

The theoretical advantages of early treatment are that organ dysfunction may be prevented, and hence progression-free survival (which incorporates organ dysfunction) is advocated as a desirable endpoint. Amongst the 21 progression events in the observation arm in the study

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Supplemental data for this article can be accessed here.

Table 1. Characteristics of Characteristics of smoldering multiple myeloma trials trials.

Description of trials	Number (%)
Randomized	10 (30.3)
Trials currently enrolling	12 (37.5)
Included non-high risk smoldering patients	6 (18.8)
Assessing regimen already studied in active myeloma	21 (65.6)
Definition of high-risk smoldering used	
Mayo-New	4 (12.9)
Mayo-Old	8 (25.8)
Spanish	2 (6.4)
Combination/other	10 (32.2)
Not reported	7 (22.6)
Primary endpoint (including co-primary)	
Safety	6 (18.8)
Response rate	13 (40.6)
Progression-free survival	10 (31.2)
Overall survival	1 (3.1)
measurable residual disease	1 (3.1)
Other	1 (3.1)
Enrolling in the United States	23 (71.9)

comparing lenalidomide to observation for SMM, 11 were bone lesions/plasmacytomas that and eight were anemia (decrease of hemoglobin of $\geq$2 g/dL) [7]. Although fractures are an important cause of morbidity and worthy of preventive strategies – the question of whether clinically significant, irreversible end-organ damage was indeed prevented by these therapies remains. Although the Spanish randomized trial that evaluated lenalidomide and dexamethasone versus observation for smoldering myeloma has indeed shown a survival benefit, two caveats must be noted. First, this trial was not adequately powered for a survival analysis, and second, as the control arm did not get prevailing standard of care in the United States at progression with very low rates of use of immunomodulatory drugs upon progression, the relevance of the findings to contemporary patients is in question [8].

Furthermore, it must be noted that these protocols require stem cell mobilization which represents a financial burden to society as well as an inconvenience to patients, for a procedure that these patients may never undertake [9]. However, the cost of stem cell mobilization and collection pales in comparison to the costs of active contemporary MM treatment. These costs are of particular concern in treating SMM, as asymptomatic individuals that may never need therapy are subjected to prolonged and expensive therapies [10].

Current definitions of SMM encompass a heterogenous group of patients, including patients whose disease process is destined to never become malignant, and simply includes disease that is similar to monoclonal gammopathy of undetermined significance, but with a larger volume of disease. However, the current definition of SMM also include patients whose disease is destined to become malignant and cause end-organ damage [11]. The current landscape of trials and recommendations for lenalidomide use as a standard of care indeed poses the risks of both over-treating patients whose disease does not need treatment, and undertreating patients who are destined to have symptomatic MM in the imminent future.

It is anticipated that in the near future, genomic identification of MM precursors that are desisted to become symptomatic can help avoid over-treatment [12]. In the interim, given that deaths related to treatment have already been reported in these trials which are recruiting asymptomatic patients [13], there is an urgent need to prioritize randomized studies with endpoints that are most relevant to patients such as quality of life and overall survival. Although non-randomized studies with a strong translational component that helps us understand the biology of SMM are important, the current landscape of duplicative, uncontrolled single-arm studies of regimens already established in MM renders asymptomatic patients that may never progress susceptible to overtreatment. Such trials may not answer the questions that are most relevant, such as whether we are simply delaying the need for further systemic treatment by administering treatment now, or whether we are truly preventing a malignancy.

Disclosure statement

Vinay Prasad reports royalties from Johns Hopkins Press, Medscape, MedPage, consulting for UnitedHealthcare, and speaking fees for Evicore. Vinay Prasad has a plenary session podcast that has Patreon backers. Vinay Prasad is funded to study low value drugs through a grant from Arnold Ventures. Aaron Goodman reports consulting for Seattle Genetics and EUSA Pharma. None of the authors have any other conflicts of interest.

References

[1] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014; 15(12):e538–e548.

[2] Lakshman A, Rajkumar SV, Buadi FK, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J. 2018;8:59.

[3] Perez-Persona E, Vidriales MB, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood. 2007;110(7):2586–2592.

[4] Hill E, Dew A, Morrison C, et al. Assessment of discordance among smoldering multiple myeloma risk models. JAMA Oncol. 2021;7(1):132–134.

[5] Kumar SK, Callander NS, Adekola K, et al. Multiple myeloma, version 3.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(12):1685–1717.

[6] Goodman AM, Kim MS, Prasad V. Persistent challenges with treating multiple myeloma early. Blood. 2021;137(4): 456–458.

[7] Lonial S, Jacobus S, Fonseca R, et al. Randomized trial of lenalidomide versus observation in smoldering multiple myeloma. J Clin Oncol. 2020;38(11):1126–1137.
[8] Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med. 2013;369(5):438–447.
[9] Ahmed N, Li L, Rojas P, et al. Significant costs and low utilization of stored peripheral blood stem cells for salvage autologous transplant in multiple myeloma patients including those meeting mSMART criteria. Bone Marrow Transplant. 2021.
[10] Rajkumar SV. Value and cost of myeloma therapy. Am Soc Clin Oncol Educ Book. 2018;38:662–666.
[11] Schmidt TM, Callander NS. Progress in the management of smoldering multiple myeloma. Curr Hematol Malig Rep. 2021;16(2):172–182.
[12] Maura F, Bolli N, Rustad EH, et al. Moving from cancer burden to cancer genomics for smoldering myeloma: a review. JAMA Oncol. 2020;6(3):425–432.
[13] Mateos M-V, Martinez-Lopez J, Rodriguez Otero P, et al. Curative strategy (GEM-CESAR) for high-risk smoldering myeloma (SMM): carfilzomib, lenalidomide and dexamethasone (KRd) as induction followed by HDT-ASCT, consolidation with Krd and maintenance with Rd. Blood. 2019; 134(Suppl. 1):781.