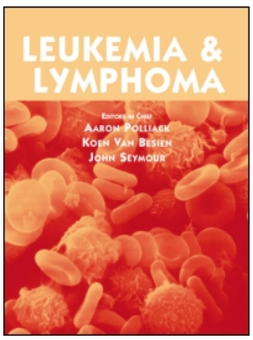

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COMMENTARY

Should high risk smoldering myeloma be treated outside a clinical trial: NO

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In this issue of Leukemia and Lymphoma, Mohyuddin and colleague examined the characteristics of 32 clinical trials evaluating patients with smoldering multiple myeloma. In virtually all the trials surrogate endpoints of response rates and progression free survival (PFS) are being used and not overall survival, quality of life, symptomatic bone disease, and irreversible rises in creatinine, which are the endpoints most relevant to patients who by definition are asymptomatic and are being asked to submit themselves to therapy [1].

One of the main challenges is simply defining what constitutes high-risk smoldering multiple myeloma. In the 2 published randomized clinical trials, different criteria were used and had very poor concordance. Individuals deemed high-risk in one criterion set were actually low risk in the second set. The overall concordance was only 28.6% suggesting that different trials will select different populations for hypothesis testing [2]. Among 38 high-risk smoldering identified by the Spanish model only 4 were high-risk by the Mayo model [3].

Only a single clinical trial has reported survival benefit in treating high-risk smoldering multiple myeloma [4]. However, one needs to look at the trial design to determine if the conduct of the trial would conform to practice standards today. This trial was performed in the era before it was recognized that high-end skeletal imaging is required for a diagnosis of smoldering multiple myeloma can be made. In other words, either whole-body MRI or PET-CT scan must be negative before a patient can be considered smoldering. In a study of PET-CT in the diagnostic evaluation of smoldering multiple myeloma, PET positivity was seen in 74 of 188 patients (40%) which by today's criteria would reclassify smoldering myeloma into active myeloma [5]. The inclusion of patients who had active multiple myeloma by today's criteria may explain the very rapid development of CRAB in patients that were randomized to placebo arm in the Spanish trial. Moreover, for patients to cross over from placebo to active therapy CARB criteria had to be fulfilled. No allowance was made for rapid change in the monoclonal protein level over time. Today the velocity of rise of the protein is often considered a criterion for intervention [6]. Delaying intervention in the face of a rapidly rising M protein may contribute to shortened survival.

A second recently published randomized trial demonstrated a progression-free survival advantage for the treated group [7]. This trial did not demonstrate survival benefit and 49 patients enrolled were low risk by the Mayo Clinic criteria. 47% of the patients had abnormal MRI raising a question as to whether they really should have been considered active multiple myeloma. The study randomized only 29 high-risk patients into groups of 15 and 14. No statistic for progression-free survival was applied possibly because the numbers were under-powered for reporting purposes. This trial also did not include time-dependent criteria based on increasing M protein or declining hemoglobin for risk assessment of evolution into active disease.

Presumably smoldering multiple myeloma represents a heterogeneous mix of patients with true multiple myeloma that is in evolution and likely would benefit from early intervention and dose patients with more indolent MGUS like biology that do not require treatment. Trials to date that use lenalidomide dexamethasone, lenalidomide, or recently daratumumab [8] likely are over-treating the patients with MGUS but severely undertreating patients with true myeloma where multiple trials have demonstrated the need for triplet or quadruple it therapy to achieve best outcomes. The rationale for using a single agent in

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Supplemental data for this article can be accessed here.

patients who are believed to truly have multiple myeloma in evolution would run the risk of selection of resistant clones [9]. Fortunately phase 2 trials are underway in an effort to aggressively manage those smoldering patients with multi-drug chemotherapy regimens including daratumumab, carfilzomib, lenalidomide, dexamethasone and stem cell transplants as are used in multiple myeloma, such as the ASCENT trial (NCT03289299) and GEM-CESAR (NCT 02415413). Phase 3 trials such as DETER-SMM (NCT03937635) and ITHICA (NCT04270409) are enrolling but lack a no therapy arm apparently having decided this question has been answered.

One must keep in mind that smoldering multiple myeloma is not a disease as patients are perfectly well. Intervention amounts to chemoprevention or adjuvant therapy and should be thought of in those terms. The goal is to develop a risk assessment that statistically marks patients for whom symptomatic disease is imminent and the risk of delaying therapy to avoid drug related symptoms is lower than the risk of developing irreversible complications from progressive disease. However, even when patients have an estimated risk of an 80% chance of developing symptomatic myeloma in 24 months this merely represents an assessment at one moment in time. This snapshot of activity is not optimal to assess our patients. It would be far better to record multiple snapshots over time to create a movie of the disease. If patients are very closely monitored for changes in the M protein, the involved light chain, the hemoglobin, and creatinine one may be able to develop a biologic pattern capable of assessing risk over time.

Finally, the agents that we are currently using are far from benign even though they may not technically represent chemotherapy. The peripheral neuropathy associated with bortezomib can be life changing for patients destined to live more than a decade. At least a third of patients develop clinically important peripheral neuropathy and although usually reversible, there remain large numbers of patients on high-dose gabapentin as well as opioids incapable of sleeping without a benzodiazepine. Although for most trials only grade 3 or 4 neuropathy is reported, grade 1 neuropathy with pain is a life changing event for patients. Venous thromboembolism even with prophylaxis can affect one patient in eight adding the burden of long-term use of anticoagulant. Virtually all patients hate dexamethasone: insomnia, mood swings, hyperirritability, and occasional hypomania affect both the patients and their entire families. The development of insulin-dependent diabetes, hypertension, cataracts, and the increased infection risk are additional morbidities these patients face. On questioning most patients will have diarrhea and fatigue which likely will be indefinite given the current trend for maintenance until progression. This is clearly justifiable in the presence of an overly diagnosed malignancy, but it becomes a separate issue in patients initially completely asymptomatic. In those patients that are transplanted and receiving lenalidomide maintenance, the risk of a second primary malignancy is doubled. Since 90% of patients with overt myeloma die of myeloma, I would consider this a justified risk. However, in an asymptomatic patient at risk, but not having developed multiple myeloma, I see an ethical issue [10].

One must be clear that support for enrollment of these patients into clinical trials is unequivocal; it is not reasonable to expect progress unless these patients are enrolled to improve outcomes for all in the future. However, the trial should provide an answer that is meaningful to patients or at least provide a steppingstone with the hope to generalize progress in therapy to the entire population. Proving that treatment lowers the M protein better than no treatment is not a meaningful answer for patients. However, outside of a clinical trial, I find it hard to justify empirically treating patients because on a given day the ratio was 20, the percentage of plasma cells was 20 and the M protein was 2 without seeing them back for 2 consecutive months to assess whether the levels of M protein, hemoglobin, and creatinine are static or evolving. For conscientious practicing oncologists, the treatment of any patient with smoldering multiple myeloma outside of a clinical trial on the 1st visit is hard to justify.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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