POINT-COUNTERPOINT

blood advances

COUNTERPOINT Timing of treatment of smoldering myeloma: delay until progression

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This article has a companion Point by Mateos and González-Calle.

The optimal approach to management of smoldering multiple myeloma (SMM) remains one of the most debated topics in myeloma today.[1,2] It has become clear over the past decade that SMM is not a single biological entity but rather a mixture of patients with incipient myeloma and those who are biologically closer to monoclonal gammopathy of undetermined significance (MGUS).[3,4] The malignant transformation of the clonal plasma cells seen in MGUS to those seen in active multiple myeloma (MM) represent a cumulative effect of changes within the plasma cell as well as the tumor microenvironment.[5] Unfortunately, there is no easy way to distinguish between these 2 groups of patients by using laboratory tests or morphologic or genomic evaluation of clonal plasma cells. In recent years, the interest in early intervention in myeloma has grown considerably for several reasons. There has been significant progress in the treatment of myeloma, with multidrug regimens providing effective disease control with very manageable toxicities.[6] This has led to a higher level of comfort with treating patients early, which is reflected in the recent revisions to the diagnostic criteria for active myeloma. In 2016, the diagnostic criteria for myeloma was revised to include biomarkers that predicted for a very high risk of progression, 80% at 2 years, a risk level that the myeloma community felt comfortable with intervention given the potential catastrophic end-organ damage that can occur in patients at the time of progression to myeloma.[7] This led to reclassification of 5% to 10% of patients previously diagnosed with SMM to be recategorized as having active MM requiring therapy. Given the fact that all patients have a preceding premalignant phase (MGUS) and that myeloma remains incurable despite the current approaches, there has been intense interest in early intervention with the hope that it could cure the disease or at the minimum delay the progression to symptomatic MM.[8] When considering intervention in SMM, it is important to keep in mind that only a proportion of patients with SMM are going to be diagnosed during this transition phase. However, one can agree that it is reasonable to hypothesize that early intervention can positively alter the natural history of the disease.

The first question is whether we should treat all patients with SMM, and the answer is clearly no. Long-term follow-up of patients with SMM has clearly shown that nearly half of patients do not progress in the first 5 years, and more importantly, one-third of patients remain progression-free at 10 years and have a progression risk that is comparable to MGUS (ie, 1% per year).[2,9] Such a strategy will clearly lead to treatment of a large number of patients who may never have required an intervention. The current treatments, while not as toxic as the older treatments, still carry a considerable amount of short- and long-term risks. The next question then should be whether we should treat the 50% of patients who are at higher risk of progression (progressing within 5 years). This would be a reasonable approach to test in a clinical trial, provided we can identify these patients with reasonable accuracy. Several risk-stratification systems have been developed to identify patients with SMM at the highest risk of progression, primarily based on tumor burden and elimination of normal plasma cells by the malignant clone (Table 1).[2,9-17] More recently, these models have been revised to account for the revised definition of SMM, but the limitations of the risk-stratification systems do elevate the risk that many patients who may have never progressed will be subjected to potentially toxic treatments. One can certainly reduce this risk by taking the subgroup of patients identified to be at the highest risk of progression in these models. Multiple small single-arm trials have demonstrated that the currently used myeloma treatment regimens can be effective against the plasma cells in these patients leading to deep responses, including minimal residual disease–negative state (Table 2).[18-23] But what we really need to see is not only a deep response or even a delay in the risk of progression to active MM but also, most importantly, an improvement in the overall survival of these patients, thus providing firm evidence of meaningful benefit. The results of the QuiRedex trial, which has been described by Mateos and González-Calle, is often highlighted as the proof of principle for early intervention in SMM.[18] However, the study fails to make a convincing argument in support of early

Table 1. Risk-stratification models for SMM

References	Risk factors	Risk groups	Progression risk
2	BMPC >10%; serum M protein >30	0 = low risk; 1 = intermediate risk; 2 = high risk	2-y progression rate (5-y TTP): low risk, 6% (15%); intermediate risk, 22% (43%); high risk: 45% (69%)
15	95% aberrant BMPC (absence of CD19 and/or CD45 expression, overexpression of CD56, or weak expression of CD38); immunoparesis of the uninvolved immunoglobulins	0 = low risk; 1 = intermediate risk; 2 = high risk	Median TTP (5-y progression rate): low risk, NR (4%); intermediate risk, 73 mo (46%); high risk, 23 mo (72%)
12	BMPC >10%, serum monoclonal protein >30; involved FLC/uninvolved FLCr >8	0 = low risk; 1 = intermediate risk; 2-3 = high risk	2-y progression rate (5-y progression rate): low risk, 12% (25%); intermediate risk, 27% (51%); high risk, 52% (76%)
17	BMPC ≥40%; involved/uninvolved FLCr ≥50; serum albumin ≥3.5 g/dL	0 = low risk; 1 = intermediate risk; 2-3 = high risk	2-y rates of progression were 16%, 44%, and 81%
9	BMPC >20%; serum monoclonal protein >2 g/dL; involved/uninvolved FLCr >20	0 = low risk; 1 = intermediate risk; 2-3 = high risk	Median TTP (mo): low risk, 109.8; intermediate risk, 67.8; high risk, 29.2

BMPC, bone marrow plasma cell percentage; FLCr, serum free light chain ratio; NR, not reported; TTP, time to progression.

intervention. A subsequent single-arm trial by Mateos et al using a more intense treatment approach and modern imaging techniques identified nearly one-third of the high-risk SMM patients considered for the trial as having active myeloma based on identification of bone lesions.[25] This clearly highlights the pitfalls of the prior study, where it would be reasonable to assume that a similar proportion of enrolled patients actually had active myeloma and the trial really represented delayed treatment of a considerable number of patients in the control (untreated) arm. This could have clearly explained the survival differences we observed in this trial and hence makes it inadequate for influencing the current clinical practice. Moreover, patients in the observation arm had to develop CRAB (hyperCalcemia, Renal insufficiency, Anemia, Bone disease) features before they would be initiated on therapy, which may be later than the typical clinical practice, where clinical features may drive the decision to initiate treatment, such as rapid doubling of M protein levels. Given these caveats, we are certainly not at a point where we can initiate therapy for a patient with high-risk SMM. However, there are several large phase 3 trials that have been completed or are in the process of being completed that will provide important confirmation if this is indeed true. Importantly these trials incorporate drug combinations or novel drugs such as monoclonal antibodies. In the current situation, we do not know if it is right to start therapy early, and we also do not know how long the treatment should be given if we were to start treating these patients. The phase 3 trial gave treatment until progression, but for a regimen like lenalidomide and dexamethasone,

Table 2. Clinical trials for smoldering myeloma

Reference	Type	Treatment arms	Best response	Time to progression
20	Single-arm phase 2 (n = 29)	Thalidomide 200 mg/d for 2 wk, and then increased as tolerated to a maximum dose of 800 mg/d	PR 34%	Median, 35 mo for PR 61 mo, MR 39 mo, and <MR 9 mo
21	Single-arm phase 2 (n = 78)	Thalidomide 200 mg/d with monthly pamidronate	PR 25%	4-y EFS 60%
22	Randomized, placebo controlled	Curcumin 4 g followed by open-phase 8 g	NR	NR
18	Phase 3 randomized, placebo controlled (n = 119)	Lenalidomide 25 mg days 1-21, dexamethasone 20 mg days 1-4 and 12-15, for 9 4-wk cycles, followed by maintenance lenalidomide 10 mg days 1-21 of each 28-d cycle for 2 y	PR 79% induction, 90% maintenance	Median NR vs 21 mo 3 y OS 94% vs 80%
23	Single-arm phase 2 (n = 12)	Eight 28-d cycles of carfilzomib 20/36 mg/m^2 on days 1, 2, 8, 9, 15, and 16; lenalidomide 25 mg on days 1-21; and dexamethasone 20/10 mg (cycles 1-4/5-8) on days 1, 2, 8, 9, 15, 16, 22, and 23; followed by 24 cycles of lenalidomide	≥VGPR 100%	NR
24	Single arm (n = 22)	6 doses of PVX-410 vaccine (subcutaneous), biweekly ± 3 21-d cycles of lenalidomide, 25 mg, orally daily every 28 d	No PR single agent, 5/12 PR in combination	9 mo, NR for combination
25	Single-arm phase 2 (n = 90)	Carfilzomib 20/36 mg/m^2 days 1, 2, 8, 9, 15, 16; lenalidomide 25 mg days 1-21; dexamethasone 40 mg days 1, 8, 15, 22; followed by single ASCT with Mel200, followed by 2 cycles of KRd consolidation, followed by maintenance lenalidomide 10 mg days 1-21, dexamethasone 20 mg days 1, 8, 15, and 22 (24 4-wk cycles)	100% PR, 90% CR	NR (PFS 94% at 28 mo)

ASCT, autologous stem cell transplant; CR, complete response; EFS, event-free survival; KRd, carfilzomib, lenalidomide, and dexamethasone; MR, minor response; PFS, progression-free survival; PR, partial response; VGPR, very good partial response.

treatment until progression has not been shown to be superior to a limited duration of therapy, even in patients with active MM.[24] Should we use a gentle approach, such as lenalidomide and dexamethasone, with the goal of delaying progression, or should we use an intense 4-drug regimen with or without transplant with the intent of cure, if possible? There are several other practical issues that need to be answered if we are to start treating these patients at some point in the future. For a patient who gets started on therapy for SMM, when do you change treatment? If you have stopped treatment after a period of time, when do you restart treatment? Do you wait for biochemical progression based on International Myeloma Working Group response criteria, or do you wait for myeloma defining events? If you wait for patients to develop end-organ damage, then would it not defeat the purpose of early intervention that was started in the first place? Are patients who are developing active myeloma eligible for clinical trials that are designed for newly diagnosed myeloma? Should these patients be considered differently?

Another important reason for not adopting this as standard practice is the potential for harm. The current treatments, while not as toxic as the older treatments, still carry a considerable amount of short- and long-term risks. Long-term treatment with lenalidomide has been associated with an increased risk of second cancers, at least in the setting of posttransplant maintenance. Steroids have been associated with a variety of long-term consequences, including diabetes, lipid abnormalities, osteoporosis, and risk of infection, among others. Bortezomib and thalidomide are both associated with neuropathy that can be quite symptomatic and sometimes not reversible. One needs to keep in mind that these patients are often younger than those with active myeloma and will survive quite a long time with newer therapies instituted at the time of MM diagnosis. As a result, the consequences of the toxicities need to be included in the equation, especially when one considers cardiac toxicity, such as that seen with carfilzomib, which may seriously compromise future treatment options. If so, how do we even justify the clinical trials? Even though the Spanish phase 3 trial did not conclusively prove the benefit of early intervention, it did allay some of the fears associated with early treatment. There was no evidence of drug resistance or lack of response to subsequent therapies used in these patients. No long-term toxicity has been observed with the use of lenalidomide and dexamethasone in the treatment group. These findings clearly alleviate some of the above concerns.

In summary, there exists no evidence to suggest that early intervention in SMM, even when limited to patients at highest risk of progression to active MM, leads to improved overall survival. This, along with the concern about long-term toxicity, argues against early treatment of patients with SMM. However, this is a compelling hypothesis that needs to be investigated, and patients with SMM should be considered for clinical trials examining early intervention when possible.

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