Timing of treatment of smoldering myeloma: early treatment

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This article has a companion Counterpoint by Kumar.

Introduction
Smoldering multiple myeloma (SMM) is an asymptomatic plasma cell disorder with a heterogeneous risk of progression to multiple myeloma (MM). Customarily, not to treat and observation until the onset of CRAB symptomatology (hypercalcemia, renal insufficiency, anemia, and bone lesions) have been considered the standard of care for SMM, partially because early intervention studies failed to show any clinical benefit and were associated with significant toxicity. However, the improvement in risk assessment and the availability of new drugs, among other achievements, have raised the question of whether early treatment should be initiated in SMM patients. In fact, the adoption of new myeloma diagnostic criteria in clinical practice implies that patients harboring any of the biomarkers that predict an ultrahigh risk of developing MM should be treated early, before end-organ damage develops. Therefore, the paradigm has already begun to change; from our point of view, and considering the evidence we present below, the definition of MM will become broader, so treatment will spread to a larger group of patients, some of whom are at an asymptomatic stage with a higher probability of a better outcome.

Selection of candidates for early treatment
When SMM is suspected, from the presence of a serum M-component ≥3 g/dL and/or ≥10% of bone marrow plasma cells (BMPCs), the first step is to rule out the presence of myeloma-defining events (MDEs), according to the most recent definition of MM. The presence of any of the biomarkers predicting imminent risk of progression to MM (≥60% of BMPCs, free light chain ratio ≥100 or ≥1 focal lesion in magnetic resonance imaging) implies that patients previously considered to have SMM must now receive early treatment, because they are no indolent at all but rather active. In addition, the use of more sensitive techniques for detecting bone disease (low-dose computed tomography or positron emission tomography–computed tomography) allows us to identify asymptomatic patients that require treatment because of the early detection of bone lesions.

Once the diagnosis of SMM has been established, an accurate risk assessment has to be done, because the management will differ depending on the risk of progression to MM. Several prognostic biomarkers have been incorporated into various risk-stratification models. The Mayo Clinic and the Spanish Myeloma Group models are the only ones that have been validated in a prospective trial (Table 1). Accordingly, we can distinguish 3 groups: (1) low risk, with a very low probability of progression at 5 years (8%); (2) intermediate risk, with a 40% probability of progression at 5 years; and (3) high risk, with a 50% probability of progression at 2 years. Approximately 14% of patients diagnosed with myeloma are SMM, and 6% are now considered MM (because of the new biomarkers and detection of early bone disease), and 5% are high-risk SMM patients and potential candidates for receiving early treatment.

Clinical benefit from early treatment
The first evidence of the clinical benefit of early treatment came from a phase 3 randomized trial (QuiRedex) that included only smoldering patients at high risk of progression to MM. This trial was conducted by the Spanish Myeloma Group and compared early treatment with lenalidomide plus dexamethasone (Rd) as induction, followed by lenalidomide alone as maintenance vs observation as a standard of care. In all, 119 high-risk SMM patients were included; after a median updated follow-up period of more than 6 years, Rd provided a clinical benefit whereby not only was the progression to MM delayed relative to observation but also survival was prolonged (median time to progression: NR vs 23 months; hazard ratio [HR], 0.24, 95% confidence interval [CI], 0.14-0.41; P < .0001; overall survival: HR, 0.43; 95% CI, 0.21-0.92; P = .02) (Table 2). Although this combination has not been approved because the trial was not designed as a registration study, the trial represents a milestone that has prompted numerous other clinical trials exploring early treatment as a strategy for SMM patients at high risk of progression. The Eastern Cooperative Oncology Group has compared lenalidomide to observation in a randomized trial, and their final results are eagerly awaited.
groups have subsequently designed clinical trials based on Rd as a backbone with novel drugs to increase the efficacy, such as carfilzomib (KRd), ixazomib (Ixa-Rd), or elotuzumab, or even single-agent monoclonal antibodies (mAbs) such as elotuzumab (anti-SLAMF7), siltuximab (anti-interleukin-6), daratumumab, or isatuximab (NCT02960555) (anti-CD38) (Table 2).

**Goals of early treatment in SMM**

The phase 3 QuirRedex trial served as the basis for several ongoing studies in which the primary objective is usually focused on delaying the progression to MM. The long-term efficacy results reported in this trial have also raised the hope that some high-risk SMM cases could be “cured” by early treatment. Actually, 2 points of view are under debate, with some researchers favoring control of the disease through continuous oral therapy and others supporting its eradication through intensive therapy. As a result, we can distinguish clinical trials of SMM based on their primary goal.

**Delivering disease progression**

Some trials have evaluated the role of mAbs and, similar to what occurs in MM, early treatment with elotuzumab in monotherapy proves not to be as effective as when it is used in combination. Dana Farber’s group is conducting a phase 2 trial evaluating the combination of elotuzumab with Rd in high-risk SMM patients and has demonstrated its efficacy (ORR, 84%) and good safety profile. Preliminary data from the CENTAURUS phase 2 study recently showed that daratumumab is active as a single agent in high-risk SMM (ORR up to 56%) and has a favorable safety profile. In addition, a long daratumumab-dosing schedule was associated with longer PFS. These results are the rationale for the AQUILA phase 3 trial, which is comparing a long-dose subcutaneous daratumumab schedule with observation. A trial evaluating the anti-CD38 mAb isatuximab in high-risk SMM is underway (NCT02960555).

Very promising results have also been presented with proteasome inhibitor combinations. Although only 12 SMM patients were treated with KRd in a phase 2 trial, all but one of them achieved an MRD-ve CR. Notably, high-risk SMM patients had deeper responses than MM patients, which could also indicate that early treatment translates into a clinical benefit.

These approaches attempting to delay progression would be appropriate for elderly high-risk SMM patients for whom the goal is to avoid the development of any MDEs. Under these circumstances, treatment should be convenient and possibly planned as continuous therapy.

**Curing the disease**

The long-term efficacy reported with Rd in high-risk SMM, together with the sustained MRD-ve rates observed in some of the aforementioned studies, provided proof of principle to underpin subsequent studies of more intensive therapeutic approaches for young high-risk SMM patients, similar to those planned for young MM cases with a “cure” (defined as an MRD-ve state sustained for at least 5 years) as the main objective. Some initiatives have followed this approach, such as those promoted by the Spanish Group’s CESAR trial, and the International Myeloma Foundation/Black Swan initiative with the ASCENT trial. Both are based on induction (KRd or KRd-daratumumab), followed by consolidation and maintenance that prolong treatment up to 2 years. Although longer follow-up is required in the CESAR trial, the results are encouraging, with a 55% MRD-ve rate after ASCT and an acceptable toxicity profile. Results from ASCENT are eagerly expected and may help clarify the role of ASCT in this group of patients.

**QoL and ethical concerns**

In general, patients with SMM are asymptomatic with good quality of life (QoL). For this reason, the risk of subjecting an asymptomatic patient to drug-related side effects and potentially impairing their QoL should be considered before initiating treatment. Early therapeutic intervention was abandoned in the past due to the potential risk of secondary leukemias with melphalan or the high incidence of peripheral neuropathy associated with thalidomide. However, current schemes with novel agents have a manageable toxicity profile (Table 2) and ongoing studies are exploring the efficacy of more convenient drugs, such as subcutaneous daratumumab, weekly carfilzomib, or oral-drug combinations, such as Ixa-Rd (NCT02916771).

It is difficult and almost unethical for doctors not to offer treatment to high-risk SMM patients in clinical practice while waiting for a definitive event to occur that will cause their QoL to deteriorate. However, if early treatment is not feasible, then the best approach should be to refer patients to centers specializing in myeloma therapy and include them in clinical trials to confirm the benefit of early treatment. In addition, this is an opportunity to conduct biological studies to improve our understanding of the disease. One of the main concerns about continuous therapy is...
Table 2. Results from clinical trials exploring early treatment in high-risk SMM

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Phase</th>
<th>Treatment</th>
<th>Follow-up, median (range), mo</th>
<th>Results</th>
<th>Safety profile (grade ≥3 AE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QuiRedex (NCT00480363)</td>
<td>3</td>
<td>Rd vs observation. Induction: 9 × 28-d cycles R 25 mg/d on d 1-21 + Dex 20 mg/d on d 1-4, 12-15. Maintenance: 2 y 28-d cycles with R 10 mg/d on d 1-21.</td>
<td>73 (66-84) n = 119. Median TTP: NR (95% CI, 47 mo to NR) vs 23 mo (95% CI, 16-31 mo); HR, 0.24 (95% CI, 0.14-0.41); P &lt; 0.0001. Median OS: NR in both arms (HR, 0.43; 95% CI, 0.21-0.82); P = 0.02</td>
<td>—</td>
<td>Infection (8%); 1 death, asthenia (8%), neutropenia (5%), and skin rash (3%)</td>
</tr>
<tr>
<td>NCT01169337</td>
<td>2/3</td>
<td>R vs observation. Ralone at 25 mg d 1-21 every 28 d.</td>
<td>17</td>
<td>Preliminary ASH 2013 meeting; n = 44; PR, 33%, SD, 58%</td>
<td>—</td>
</tr>
<tr>
<td>NCT02279394</td>
<td>2</td>
<td>Elotuzumb + Rd. Elotuzumab 10 mg/kg IV d 1, 8, 15, and 22. Cycles 1 and 2, 10 mg/kg IV d 1 and 15; cycles 3-8, lenalidomide 25 mg d 21; cycles 1-24, Dex 40 mg oral d 1, 8, 15, and 22; cycles 1 and 2, 40 mg oral d 1, 8, and 15 in cycles 3-8.</td>
<td>— n = 31. ORR: 84%; CR: 7%; VGPR: 36%; PR: 42%; clinical benefit rate: 100%.</td>
<td>—</td>
<td>Hypophosphatemia (30%), neutropenia (14%), infection (12%), anemia (2%), pulmonary embolism (2%), rash (4%), and diarrhea (2%)</td>
</tr>
<tr>
<td>NCT01441973</td>
<td>2</td>
<td>Elotuzumab. Cohort 20 mg/kg IV: cycle 1, d 1 and 8; monthly thereafter; cohort 10 mg/kg: cycles 1 and 2 weekly; every 2 wk thereafter.</td>
<td>28</td>
<td>n = 31. ORR (90% CI) 10%; 2-y PFS: 69% (52-81%).</td>
<td>—</td>
</tr>
<tr>
<td>NCT01484275</td>
<td>2</td>
<td>Siltuximab vs placebo. 15 mg/kg siltuximab or placebo 1-h IV infusion every 4 wk until disease progression to MM.</td>
<td>29.2</td>
<td>n = 31. ORR (90% CI) 10%; 2-y PFS: 84.5% (95% CI, 68.6-92.8) vs 74.4% (95% CI, 57.3-85.5).</td>
<td>—</td>
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<tr>
<td>CENTAURUS (NCT02316106)</td>
<td>2</td>
<td>Daratumumab. 16 mg/kg IV in 8-wk cycles. Long: every wk in cycle 1, every other wk in cycles 2 and 3, every 4 wk in cycles 4-7, and every 8 wk up to cycle 20. Intermediate: every wk in cycle 1 and every 8 wk up to cycle 20. Short: every wk for 1 cycle.</td>
<td>15.8 (0.0-23.6) n = 41 in each arm; ORR: 56%/54%/38%; 12-mo PFS, 95%/88%/81%</td>
<td>—</td>
<td>Infection (&lt;5% in all arms)</td>
</tr>
<tr>
<td>NCT01572480</td>
<td>2</td>
<td>Carfilzomib + Rd. Eight 28-d cycles of carfilzomib 2036 mg/m² on d 1, 2, 8, 9, 15, and 16; lenalidomide 25 mg on d 1-21; and Dex 20/10 mg (cycles 1-4/5-8) on days 1, 2, 8, 9, 15, 16, 22, and 23 + 2 y R maintenance.</td>
<td>15.9</td>
<td>n = 12; CR, 100%; MRD (flow), 92%</td>
<td>—</td>
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<tr>
<td>CESAR (NCT02415413)</td>
<td>2</td>
<td>Induction: KRd × 6 cycles (carfilzomib IV/ 2036 mg/m² d 1, 2, 8, 9, 15, and 16/lenalidomide 25 mg d 1-21/Dex 40 mg d 1, 8, 15, and 22). ASCT: consolidation, KRd × 2 cycles; maintenance, Rd × 2 cycles.</td>
<td>17 (5-36) n = 90; efficacy after ASCT (+100; ORR, 100%; ≥CR, 63%; VGPR, 23%; MRD-ve rate (flow), 55%</td>
<td>—</td>
<td>Neutropenia (6%), thrombocytopenia (11%), infections (18%), and skin rash (9%)</td>
</tr>
</tbody>
</table>

AE, adverse event; ASCT, autologous stem cell transplantation; ASH, American Society of Hematology; CR, complete response; Dex, dexamethasone; flow, flow cytometry; MRD, minimal residual disease; MRD-ve, minimal residual disease negative; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R, lenalidomide; SD, stable disease; VGPR, very good partial response.
the acquisition of treatment resistance. Although more biological studies are required to understand how clonal evolution and the immune system operate under treatment selection, an updated analysis of the QuiRedex trial showed that early treatment did not induce more resistant relapses.20

Conclusions

In our opinion, 2 strands of evidence provide increasing support for early treatment of patients with SMM: (1) randomized trials have shown a clinical benefit, and the treatment of asymptomatic patients seems to be more efficacious than the same combinations used in symptomatic patients; and (2) new projects focusing on risk stratification will allow us to accurately identify asymptomatic patients who will be considered to have MM, so criteria for defining MM will be broadened, enabling asymptomatic patients to be treated like myeloma patients so that their disease is better controlled or even cured.

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Authorship

Contribution: V.G.-C. and M.-V.M. drafted the article and M.-V.M. revised it critically, giving final approval of the version to be submitted.

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