COUNTERPOINTS

Current Controversies in Hematology and Oncology

Do Patients With Multiple Myeloma Need Maintenance Treatment?

Multiple myeloma is an incurable disease, and patients who respond to treatment eventually relapse—which makes long-term maintenance therapy an appealing option. But is a treatment with an unclear effect on overall survival worth the side effects and financial cost? In this month's Counterpoints, Drs James R. Berenson and Claudia Andreu-Vieyra make the case for maintenance treatment, whereas Drs David H. Vesole and David S. Siegel take a more cautious approach.

Yes, But the Proper Candidates and Schedule Must Be Determined

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Multiple myeloma (MM) is the most common primary malignancy of the bone marrow.[1] Although the recent approvals of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) have resulted in a significant improvement in the overall survival (OS) of MM patients, the disease remains incurable and patients eventually relapse.[2,3]

Long-term maintenance therapy has been suggested as a viable approach to delaying relapse, resulting in longer progression-free survival (PFS) and, more importantly, OS.[4] Ideally, maintenance therapy should sustain treatment responses, have good safety and tolerability profiles in long-term use, and be convenient for patients. Importantly, it should not reduce the efficacy or preclude the use of other drugs in future treatments.

Trials in the Frontline Setting

Almost all of the data addressing the use of maintenance therapy come from trials in the frontline setting. Interferon alfa (IFN-α) and corticosteroids were among the first drugs tested. IFN-α has been shown to increase OS

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No, Maintenance Treatment Should Not Be Used Outside Clinical Trials

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Maintenance therapy in MM has been under investigation for decades. Before the introduction of novel therapies (PIs and IMiDs), maintenance therapy using corticosteroids, interferon, or chemotherapy was deemed too toxic, ineffective, or minimally effective.

Immunomodulatory Drugs

Patients treated with thalidomide, the first of the 3 available IMiDs, have improved PFS in most trials and OS in some trials. The agent is poorly tolerated, however, leading to high discontinuation rates.[1,2] Further, questions about the lack of availability of thalidomide as salvage (crossover) in the control arm of these trials has certainly made it difficult to interpret the concept of maintenance vs salvage. This is a problem that has plagued virtually all

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Yes, But the Proper Candidates and Schedule Must Be Determined *(cont)*

by 7.0 months and duration of remission by 4.4 months.[5] A later analysis of quality time without disease relapse or toxicity demonstrated that IFN-α–treated patients gained an average of 9.8 months without disease relapse and 5.8 months of OS vs the control arm; however, they also experienced an average of 4 months of moderate- to high-grade toxicity.[6] As a result, IFN-α use in the maintenance setting has largely been abandoned.

Among patients responding to conventional chemotherapy, maintenance with oral prednisone (50 mg every other day) was shown to improve PFS by 9 months and OS by 11 months, compared with 10 mg of prednisone every other day.[7] Although well-tolerated in this study, chronic use of corticosteroids is associated with long-term toxicities, including hyperglycemia, osteoporosis, weight gain, muscle weakness, and infections.

IMiDs, PIs, and bisphosphonates also have been evaluated as maintenance therapy. Treatment with the IMiD thalidomide, alone or with corticosteroids, has yielded mixed results. In 1 randomized trial, thalidomide administered at various doses from induction to maintenance produced no improvement in PFS compared with the control arm.[8] Better results were achieved in 2 trials evaluating thalidomide at 50 mg daily. In 1 study, patients were randomized to receive induction with doxorubicin, dexamethasone, and either thalidomide or vincristine, and then autologous stem cell transplantation followed by maintenance therapy with thalidomide or IFN-α, respectively.[9] In the other trial, patients received induction with intensive or nonintensive therapy and were randomly assigned to receive maintenance with either thalidomide or placebo.[10] In both studies, thalidomide prolonged event-free survival (EFS) and/or PFS.[9,10] Compared with corticosteroids alone, thalidomide with corticosteroids improved PFS[11,12] and also OS, when the combination was given following high-dose therapy.[13] However, this latter trial did not have a crossover design, and few patients in the corticosteroid-alone arm received thalidomide following disease progression. Long-term thalidomide use was associated with significant toxicity in these trials, especially peripheral neuropathy (PN) and somnolence, which often led to dose reductions and treatment discontinuation.[8-13] Similar results were observed in transplant-ineligible patients treated with thalidomide alone or in combination with IFN-α.[14,15] Thus, despite its convenient route of administration (oral) and its beneficial effect on PFS, thalidomide maintenance has largely been abandoned because of its significant tolerability issues.

Treatment of MM patients with lenalidomide (Revlimid, Celgene) maintenance in both the transplant and transplant-ineligible settings has shown consistent improvement in PFS and, in some studies, OS.[16-20] The agent was used alone in some trials and was combined with oral dexamethasone in others, which makes it difficult to determine the relative contribution of lenalidomide to the improved outcomes observed among patients receiving the combination. Unfortunately, lenalidomide also has been associated with an increased risk of second primary malignancies, especially leukemia and lymphoma, but these risks are far surpassed by its benefits.[16] Notably, neurologic toxicity with this oral agent occurs infrequently even with long-term use, making it a better therapeutic option than thalidomide in the maintenance setting.

Nitrogen-containing bisphosphonates, such as pamidronate and zoledronic acid, are used to reduce the risk of skeletal-related events in MM patients, but they also have antitumor properties.[20,21] In 1 study, patients were randomly assigned to receive pamidronate alone (90 mg per month), pamidronate and thalidomide (400 mg daily), or no maintenance therapy following autologous stem cell transplantation. Improvements in both EFS and OS were observed in patients receiving the combination compared with pamidronate alone or no maintenance therapy.[14] There was a high incidence of thalidomide-induced PN, which resulted in frequent treatment discontinuation. Another study compared long-term zoledronic or clodronic acid administered with and following intensive or nonintensive therapy.[21] Intravenous zoledronic acid (4 mg) was administered every 3 to 4 weeks, whereas oral clodronic acid (1600 mg) was given daily.[21] Zoledronic acid significantly extended OS by 5.5 months and PFS by 2 months compared with clodronic acid, but it was also associated with a higher proportion of patients developing treatment-induced osteonecrosis of the jaw.[21] It is unclear whether the benefit observed with zoledronic acid was the result of

> Patients who do not show disease progression should receive maintenance therapy.

the initial treatment or from its use following induction therapy. Further studies are needed to determine this.

The efficacy of maintenance therapy with the PI bortezomib (Velcade, Millennium Pharmaceuticals) remains unclear. In transplant-ineligible patients, a trial evaluating maintenance with bortezomib and thalidomide (VT) vs bortezomib and prednisone after induction with bortezomib, prednisone, and either melphalan (VMP) or thalidomide (VTP) demonstrated no significant differences in OS between arms.[22] Another study randomly assigned patients to receive induction with VMP and thalidomide (VMPT) followed by maintenance with VT, or induction with VMP followed by no maintenance.[23] OS and PFS were significantly improved among patients receiving the VMP-VT regimen, even though VT-induced toxicities limited long-term treatment.[23] However, it is difficult to determine whether this advantage is the result of the induction or maintenance therapies. Bortezomib alone following induction with bortezomib and dexamethasone (VD), VMP, or bortezomib, dexamethasone, and thalidomide (VTD) did not significantly improve PFS or OS.[24] Maintenance with bortezomib also has been explored in transplant-eligible patients. In 1 trial, patients were randomly assigned to receive induction with vincristine or bortezomib in combination with doxorubicin and dexamethasone (VAD or PAD), followed by high-dose melphalan and autologous stem cell transplantation.[25] Patients induced with VAD received maintenance with thalidomide (VAD-T), whereas those induced with PAD received bortezomib (PAD-P).[25] At 5 years, PAD extended PFS by 7 months and OS by 6 percentage points compared with VAD.[25] In another study, patients were induced with 3 different regimens and then randomized to receive maintenance with VT, thalidomide alone, or IFN-α2b alone.[26] From the onset of maintenance, VT resulted in significantly longer PFS compared with thalidomide or IFN-α2b; however, no significant differences were observed in OS.[26] Based on these trials, the role of bortezomib in maintenance therapy is promising but still unclear.

Newer agents, such as the IMiD pomalidomide (Pomalyst, Celgene), the PI carfilzomib (Kyprolis, Onyx), and the investigational oral PI ixazomib, may prove to be better maintenance options, but need to be further evaluated.

Trials in the Salvage Setting

Less is known about the role of maintenance therapy in the salvage setting. A single-arm trial investigated treatment with bortezomib (1.3 mg/m^2 on days 1 and 15 of a 28-day cycle) and dexamethasone (20 mg daily on days 1-2 and 15-16) for patients who responded to bortezomib.[27] The median time to progression was 16 months.[27]

Discussion

The maintenance studies described here have examined many different types of agents and agent combinations, using a variety of doses and schedules for varying lengths of time. However, no randomized trial has compared maintenance therapy for a fixed number of cycles with therapy until disease progression, and only a few studies have evaluated different maintenance regimens as the only randomization variable. As a result, no standards exist for the implementation of maintenance therapy.[4]

This does not mean that its use should be avoided, however. Most studies have shown improvement in PFS, and some studies have shown improvement in OS. The problem is that the risk of toxicity increases with long-term treatment, which is why the benefits of maintenance may not outweigh the risks for certain drugs and patients. Therefore, it is essential to identify the right agent or agents, dose, and schedule for each patient. Better clinical trial designs are needed to understand the most effective way to administer these agents in the maintenance setting.

Recommendation

It is our recommendation that all patients who do not show disease progression should receive maintenance therapy with the same agents used during their treatment. One exception is chemotherapeutic agents, which should be discontinued. Maintenance agents are typically administered at lower doses or less frequently than therapeutic doses, or in combination with corticosteroids. For instance, bortezomib is given every other week instead of 4 times monthly and IMiDs are continued along with corticosteroids if corticosteroids were part of the patient's treatment regimen.

It is becoming increasingly clear that discontinuation of effective therapy only hastens the development of disease progression. As patients with MM continue to exhibit better outcomes with the ever-increasing number of available therapeutic options, it becomes imperative to develop a personalized treatment approach not only for induction therapy but also in the maintenance setting.

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No, Maintenance Treatment Should Not Be Used Outside Clinical Trials *(cont)*

trials of IMiDs and PIs for maintenance, and it clouds any interpretation of OS.

Maintenance therapy with the IMiD lenalidomide has been the focus of more recent studies. In the 1 large randomized controlled study in transplant-ineligible patients, in which lenalidomide maintenance was compared with observation, the lenalidomide group demonstrated superior median PFS (31 vs 14 months) but no improvement in OS (longer follow-up is required).[3] Interestingly, although the worldwide MM community has shied away from thalidomide owing to toxicities associated with its use and the perception that thalidomide is a less effective IMiD than lenalidomide, the Dutch-Belgian Cooperative Trial Group for Hematology Oncology/Nordic Myeloma Study Group (HOVON/NMSG) compared thalidomide with lenalidomide. At the December 2014 American Society of Hematology (ASH) meeting, this group reported on a large randomized clinical trial that compared melphalan/prednisone/thalidomide plus thalidomide maintenance (MPT-T) vs melphalan/prednisone/lenalidomide plus lenalidomide maintenance (MPR-R).[4] Although the anticipated outcome was that the MPR-R would be superior to MPT-T, this was not the case. Indeed, there was no significant difference in the overall response rate (ORR), PFS, or OS. Further, these comparable results were observed with a median duration of 5 months for thalidomide maintenance vs 16 months for lenalidomide maintenance.

In the posttransplant setting, it is clear from 3 randomized trials that lenalidomide maintenance provides a 14- to 20-month improvement in PFS compared with observation.[5-7] However, only the CALGB (Cancer and Leukemia Group B) 100104 trial, in a retrospective subgroup analysis, demonstrated an improvement in OS. The CALGB trial attempted to address the management of MM when the tumor burden has been maximally cytoreduced, a point in the natural history of the disease when the MM might be more sensitive to the immunomodulatory and tumoricidal qualities of IMiDs. Unfortunately, this trial was not designed to answer the critical OS question and was instead powered to address PFS as the primary endpoint. Because it became clear early in the trial that PFS was dramatically improved, a crossover to the maintenance arm was mandated. This "cheated" the control arm out of the opportunity to be salvaged with lenalidomide at the time of disease progression without the prior selection of resistance. Perhaps equally importantly, it deterred investigators from using lenalidomide-based regimens as salvage. Further, maintenance therapy may be associated with shorter second remission duration (PFS2), thus explaining the lack of an improvement in OS.[8] A meta-analysis of 4 randomized lenalidomide maintenance trials confirmed the improvement in PFS but only a trend in OS.[9] It should be noted that in most of these trials, lenalidomide was not readily available as salvage therapy (crossover), thus obfuscating the OS endpoint—which is similar to findings reported with thalidomide. This improvement in PFS comes with absolute or potential disadvantages: (1) at least a 2- to 3-fold increase in the risk of second primary malignancies; (2) an approximate 15% discontinuation rate due to toxicities (particularly myelosuppression); (3) the generation of lenalidomide-resistant clones by low-dose, subtherapeutic lenalidomide administration, negating the potential future use of lenalidomide for antimyeloma therapy; (4) shorter duration of PFS2 in patients with prior lenalidomide exposure; and (5) the high cost—financial and otherwise—to the patient and health care system (especially in the absence of clear improvement in OS).

> Maintenance therapy should continue to be considered only in the context of clinical trials.

Proteasome Inhibitors

PIs as a maintenance strategy in the nontransplant setting have not been evaluated as a single agent compared with observation in randomized trials. Data from the Spanish Myeloma Group reveal that the combination of bortezomib or thalidomide and corticosteroids is superior to historical controls.[10] At the December 2014 ASH meeting, Kumar and colleagues presented an abstract on ixazomib, an experimental oral PI, in combination with lenalidomide and dexamethasone induction therapy with ixazomib maintenance. They reported good tolerability and improvement in the depth of the response. There is an ongoing phase 3 trial of ixazomib vs observation. In the transplant setting, the HOVON/German Multicenter Myeloma Group (GMMG) conducted a randomized trial that found that bortezomib-based induction followed by transplant with bortezomib maintenance provided a superior PFS and OS vs nonbortezomib induction followed

by transplant with thalidomide maintenance.[11] The Spanish Myeloma Group completed a 3-arm posttransplant maintenance trial in standard-risk patients that compared interferon vs thalidomide vs thalidomide/bortezomib. This trial demonstrated an improvement in PFS but not OS in the thalidomide/bortezomib cohort. In summary, PIs appear promising for maintenance after both induction and transplant.

Additional Considerations

Another area of clinical pursuit is the importance and impact of consolidation prior to maintenance therapy. There are trials reporting the use of lenalidomide, bortezomib, lenalidomide/bortezomib/dexamethasone, and bortezomib/thalidomide/dexamethasone vs thalidomide/dexamethasone. Virtually all of these trials show improvement in the depth of response, but the ultimate improvement in PFS and OS has yet to be determined. Many of the current transplant trials, such as the BMT CTN (Blood and Marrow Transplant Clinical Trials Network) 0702 and the IFM/DFCI (Intergroupe Francophone du Myélome/Dana-Farber Cancer Institute) are incorporating consolidation strategies, usually PI/IMiD/corticosteroid for 2 to 4 cycles followed by lenalidomide maintenance therapy.

An additional area of controversy is the duration of maintenance therapy. Most of the US trials continue lenalidomide until intolerance or progression, whereas the IFM limits lenalidomide to 1 year. The IFM opines that the increased duration of lenalidomide exposure is associated with an increase in second primary malignancies, although this was not observed in the CALGB trial. The current IFM/DFCI trial compares not only early vs late transplantation, but 1-year maintenance (IFM) vs continuous maintenance (DFCI).

The determination of which patients benefit from consolidation/maintenance therapy has yet to be defined. The CALGB study, however, showed that all subgroups benefited from maintenance lenalidomide: complete vs partial remission, and prior lenalidomide–treated vs lenalidomide-naive. One of the areas of intense interest in the MM community is the impact of minimal residual disease (MRD) in MM, either by multiparameter flow cytometric analysis or by the more cumbersome and expensive polymerase chain reaction analysis. Recent studies have shown that patients achieving MRD have improved PFS.[12] Unanswered questions regarding MRD include the following: whether patients achieving MRD before transplant benefit from transplant, whether patients achieving MRD after transplant require consolidation and/or maintenance, and whether maintenance can be discontinued once MRD has been achieved. Clinical trials are being designed to answer these important questions.

A persistent thorn is embedded in our collective approach to high-risk patients, and their optimal treatment remains a conundrum in the MM community. The concept of "more is better" does not appear to be true in this population of approximately 20% of MM patients. The most intense treatment approach, pioneered by the Arkansas group, includes tandem autologous transplant, a year of consolidation chemotherapy, and maintenance with a PI/IMiD/corticosteroid regimen.[13] The high-risk patients had dismal outcomes, with a median PFS of 2 to 4 years. Data also suggest that IMiD-based maintenance therapy may be contraindicated in high-risk patients: the MRC (Medical Research Council) IX trial showed that thalidomide maintenance in the high-risk subset resulted in significantly inferior OS. Although thalidomide is not lenalidomide, it certainly raises questions about the concept of low-dose IMiD therapy.[2]

Currently, there are no data on maintenance therapy following salvage transplant. This will be evaluated in an upcoming BMT CTN trial.

The use of maintenance therapy after allogeneic transplant is sparse. There are 2 small lenalidomide-based maintenance trials. The HOVON trial was discontinued early owing to toxicities, particularly an increase in the incidence of graft-versus-host disease (GVHD).[14] The use of bortezomib has not been evaluated in formal maintenance trials. In preclinical models, bortezomib appears to decrease the GVHD effect without compromising the graft-vs-myeloma effect. The randomized phase 2 BMT CTN 1302 trial will evaluate ixazomib vs observation in high-risk patients following allogeneic transplant.

Recommendations

The International Myeloma Working Group (IMWG) has reviewed the literature and published a consensus statement: "Maintenance treatment can be associated with significant side effects and none of the drugs evaluated is approved for maintenance therapy. Treatment decisions for individual patients must balance potential benefits and risks carefully, as a widely agreed upon standard is not established."[15] In the United Kingdom, the Myeloma Forum writes: "Despite the promising data, the optimal use of consolidation and maintenance treatment in terms of regimen, dose and duration has yet to be defined. Given the evidence to date, the UK Myeloma Forum believes that both maintenance and consolidation therapy should be considered as treatment options for patients with MM. Patients should be encouraged to [enroll] in clinical studies."[16]

For better or worse, almost all US-based transplant centers have incorporated lenalidomide maintenance therapy into their treatment algorithm after autologous

transplantation, even though it is not approved by the US Food and Drug Administration for this indication and is not recommended by the IMWG or the UK Myeloma Forum. Although it is clear that PFS is improved, it remains to be determined whether this results in improved OS or quality of life, and whether it is indicated for high-risk patients, after consolidation, or in MRD-negative patients. The inclusion of maintenance in trials that are designed to answer other questions (eg, 1 transplant vs 2, early transplant vs late, carfilzomib/lenalidomide/dexamethasone vs bortezomib/lenalidomide/dexamethasone as induction) profoundly compromises the ability of these trials to answer questions in a timely fashion or to answer these questions at all.

Conclusion

There is irrefutable evidence that maintenance therapy prolongs remission duration, but it is not clear whether this improvement in remission duration outweighs the disadvantages. Therefore, at this time maintenance therapy should continue to be considered only in the context of clinical trials whose goal is to answer important maintenance-related questions. For those practitioners who prescribe maintenance therapy or those patients who wish to receive maintenance therapy outside of a clinical trial, it is the responsibility of the medical provider to counsel the patient about the risks/benefits so that an informed decision can be determined.

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"Counterpoints" is a section in *Clinical Advances in Hematology & Oncology* in which we address clinical controversies and other questions of importance to oncologists and hematologists. We feature between 2 and 8 panelists for each question.

What topics would you like to see addressed in future issues? Please send your ideas to editor@clinicaladvances.com.