In high-risk SMM patients, delayed treatment resulted in early progression to symptomatic disease (median 25 months), while lenalidomide-dexamethasone induction followed by lenalidomide maintenance significantly prolonged the TTP (HR: 6.2), with a trend to improved 3-year OS (p=0.05). Tolerability was acceptable and no safety warnings regarding SPM exist.

3. Pomalidomide + low-dose dexamethasone clinically active in advanced, refractory MM

Richardson PG, Siegel DS, Vij R et al. Randomized, open label Phase/2 study of pomalidomide (Pom) alone or in combination with low-dose dexamethasone (LoDex) in patients with relapsed and refractory multiple myeloma (RRMM) who have received prior treatment that includes Len and bortezomib (Bort): Phase 2 results. ASH 2011. Abstract 634.

This multicentre Phase I/II study investigated the safety and efficacy of pomalidomide alone or in combination with low-dose dexamethasone (pomalidomide+LoDex) for patients with RRMM who had received both bortezomib and lenalidomide. The primary endpoint was PFS. A total of 221 patients were enrolled (median 5 prior therapies; median treatment duration 5.0 months); approximately three-quarters of the patients in both groups had prior autologous stem cell transplantation (ASCT). Patients were refractory to...
lenalidomide (pomalidomide+LoDex 77% vs pomalidomide alone 79%), bortezomib (73% vs 69%), or both drugs (61% vs 59%). Among patients who were randomized to receive pomalidomide alone, 56% subsequently went on to receive pomalidomide+LoDex due to progressive disease (PD) as per protocol. Overall response rates were 13% and 34% for pomalidomide alone and pomalidomide + LoDex respectively. PFS in pomalidomide+LoDex vs pomalidomide alone is summarized in Figure 1.

The authors concluded that pomalidomide (4 mg/day, 1–21 days of each 28-day cycle) + LoDex demonstrates clinical activity and is generally well tolerated in patients with advanced MM who have received multiple prior therapies and are refractory to both lenalidomide and bortezomib.

4. High response to carfilzomib in bortezomib-naive patients with RRMM


**COMMENTARY:** Over the past decade, the addition of the proteasome inhibitor bortezomib and the immunomodulatory drugs lenalidomide and thalidomide to the armamentarium in the treatment of MM has resulted in improved survival for patients, as demonstrated in multiple jurisdictions across the world and validated in Canada with data from British Columbia. Unfortunately, myeloma remains incurable there is still much room for improvement. Although there has been a growing understanding of the appropriate use and side effects of the available novel agents, expanding indications and an appreciation of long-term effects continue to be fertile grounds for research. At this year’s ASH meeting in San Diego there was further validation of the benefit of these novel agents as well as research into the refinement of their use. There was also research presented regarding even newer agents that will likely come to general use in the future, possibly resulting in further improvements in the survival and management of patients with MM.

**VALIDATION OF CURRENT APPROACHES**

Until recently, the combination of MP has been the standard treatment of newly diagnosed patients with MM who were not eligible for ASCT. The VISTA trial demonstrated that the combination of MPV was superior with improved PFS and OS. This trial as well as other trials looking at the combination of MP + thalidomide (MPT) have shifted the paradigm such that patients who are not eligible for transplant should be treated with MP plus a novel agent as initial therapy. Early use of the novel agents leads to improved survival, which cannot be recovered if use of the novel agent is delayed beyond initial therapy. At this year’s ASH meeting, updated analysis of the VISTA trial confirmed the continued benefit of adding a novel agent at initial treatment.

It is reassuring that the investigators have not seen an increased risk of SPMs. At the current time, the issue of SPMs is under significant scrutiny given the possible increased risks with immunomodulatory drugs in newly diagnosed MM patients. Research presented at ASH suggests that the risk of SPMs may not be significantly more elevated than expected in patients receiving lenalidomide as part of initial therapy. These results are particularly important as the myeloma community anxiously awaits the results of the MM-020 (FIRST) trial. This 3-armed trial comparing the use of MPT vs lenalidomide + dexamethasone for 18 months vs lenalidomide + dexamethasone until progression has completed enrolment and interim analysis will hopefully be presented in the near future. This trial may demonstrate that melphalan is not necessary as a part of initial therapy in the era of novel agents, and it will be reassuring to know that the risks of SPMs do not outweigh the benefits of the early use of lenalidomide.

**REFINEMENT OF TREATMENT APPROACHES**

Currently, patients with SMM (asymptomatic MM) require no treatment and only close followup. Approximately 50% will develop active MM or amyloidosis by 5 years and 66% at 10 years. The trial by Mateos et al enrolled patients who were at highest risk of progression and randomized them to treatment with lenalidomide + dexamethasone for 9 months followed by lenalidomide maintenance vs observation. Remarkably, patients in the treatment arm had significantly improved PFS and a borderline significant increase in 3-year OS (p=0.05) after only 22 months of followup. Treatment was well tolerated. This trial has generated much excitement as it may be practice-changing, but questions remain. First, it is uncertain why the observation arm has so many early deaths. Second, in patients who would be expected to have a prolonged survival, long-term therapy with lenalidomide may have consequences that are currently unknown. As mentioned previously, the issue of SPMs is currently being studied with great interest in MM. Finally, there remain...
What these studies showed

• Bortezomib + melphalan + prednisone (VMP) combination therapy results in significant improvement in survival vs standard of melphalan + prednisone for newly diagnosed transplant-ineligible patients with MM.

• Patients with SMM require close monitoring for possible progression to MM and to determine if treatment is required.

• Patients who have progressed after exposure to bortezomib and an immunomodulatory drug have short median survival.

What these studies showed

• MPV continues to show improved PFS and OS after median followup of 5 years. SPMs were not increased.

• Patients with high-risk SMM treated with lenalidomide and dexamethasone followed by lenalidomide maintenance had significantly improved PFS and borderline significant OS vs observation.

• Pomalidomide and dexamethasone have significant activity in patients who have progressed following exposure to bortezomib and an immunomodulatory drug.

• Carfilzomib has significant activity in patient with relapsed/refractory, bortezomib-naive patients.

Next Steps

• The Phase III MM-020 trial is anxiously awaited to see if there is another option in the standard treatment of newly diagnosed transplant-ineligible patients.

• Careful review will be required to determine if the criteria for SMM requires further refinement or if treatment should be given to patients with high-risk SMM.

• Phase III trials are awaited to determine if newer agents such as pomalidomide and carfilzomib can be added to the list of readily-available novel agents in the fight against MM.

Newer Agents for Future Use

Although survival has improved for patients with MM, most will eventually die of this disease. In particular, patients who have progressed after exposure to bortezomib and thalidomide or lenalidomide, called “double refractory,” do particularly poorly, with a median OS of 9 months. For this reason there continues to be significant research in developing new agents. Newer classes of molecules being studied include histone deacetylase (HDAC) inhibitors and monoclonal antibodies. Along with the investigations of these new classes of drugs, there continues to be research in the next generation of immunomodulatory drugs and proteasome inhibitors as well. Two of the most promising agents, which are the most mature in their clinical development and most likely to be approved for MM in the not-too-distant future, are pomalidomide and carfilzomib.

Pomalidomide is another immunomodulatory drug being studied in the treatment of MM. At this year’s ASH meeting there were a number of abstracts reporting on the use of this agent, including the IFM 2009-02 study. The abstract by Richardson et al demonstrates that pomalidomide was well tolerated and, in combination with dexamethasone, produced impressive response rates (ORR=34%) and survival benefit (median of 14.4 months) in heavily pretreated patients. Such patients typically have limited options and tend to tolerate treatment poorly. Based upon the results of this and other trials, there is currently a Phase III trial testing pomalidomide + LoDex vs high-dose dexamethasone alone for patients who are double refractory (MM-003 trial). This pivotal trial should demonstrate the true advantage of the use of pomalidomide in patients who do not have a standard option after previous exposure to lenalidomide or thalidomide and a proteasome inhibitor. The interest generated by pomalidomide in the myeloma community can be further appreciated by the number of abstracts presented that have looked at pomalidomide + other agents such as cyclophosphamide and clarithromycin. These combinations demonstrate the faith the myeloma community has in the activity of the drug as well as its tolerability, which makes its use in combinations possible.

Carfilzomib is the other drug that holds great promise for use in the near future. It is an epoxyketone-based proteasome inhibitor that irreversibly binds to the proteasome. Recent studies have demonstrated that this drug has remarkable activity and is extremely well tolerated. Importantly, PN is not a significant adverse effect of this drug even for patients who already suffer from preexisting neuropathy. Carfilzomib has been studied in a Phase II study (PX-171-003A1) that enrolled patients with myeloma previously treated with bortezomib and an immunomodulatory drug. This study revealed a 24% response rate and duration of remission of 7.4 months. With these results, carfilzomib may be more effective than bortezomib, with reduced side effects. The trial by Vij et al revealed that in bortezomib-naive patients, single-agent carfilzomib had significant activity of 42% and 52% in the 2 cohorts. Combinations such as carfilzomib, lenalidomide and dexamethasone have recently been demonstrated to produce responses in 100% of newly-diagnosed MM patients. Recently Onyx Pharmaceuticals has been granted “standard review designation” for its recent New Drug
Application for carfilzomib to the US Food and Drug Administration (FDA). Should the review be positive, carfilzomib may be marketed in the US. The myeloma community is cautiously hopeful that carfilzomib will be available for general use in the near future.

At this year’s ASH meeting, research was presented that gave us snapshots into how we are doing and what the future holds.

- Reassuringly, the VMP combination continues to show survival advantages.
- Lenalidomide demonstrates promising activity in SMM, which may lead to a paradigm shift in the diagnosis and treatment of this disease.
- Pomalidomide and carfilzomib continue to demonstrate promise as treatments that may become routinely available due to their efficacy and relative safety.
- Although the battle against myeloma is far from over, the future holds much hope.

References

Disclosure
Dr. Song has received honoraria and served on advisory boards for Celgene Inc., Janssen and Onyx Pharmaceuticals.