

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Frontline Regimens for Multiple Myeloma Patients

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H&O What is the standard of care for multiple myeloma (MM) patients? What are the response rates we see with this treatment?

SL The standard frontline therapy for newly diagnosed MM patients is a moving target. Historically, the strategies have been divided into those for transplant eligible versus non-transplant eligible patient groups, and for the sake of this discussion, we will continue that somewhat arbitrary separation.

Among patients who are not eligible for transplant, the regimens with the most phase III data supporting their use include MPT (melphalan, prednisone, and thalidomide [Thalomid, Celgene]), MPV (melphalan, prednisone, and bortezomib [Velcade, Millennium]), and RD (lenalidomide [Revlimid, Celgene] and dexamethasone). Among patients in this category, trials have demonstrated overall response rates of between 60–80% for combinations including a novel agent and MP as compared with the historical standard of MP, with which the overall response rate is only 30–40%. Interestingly, the complete response (CR) rate for MP plus a novel agent is also higher (15–35%) compared with MP alone (5%). While CR may not necessarily be the only important endpoint among older patients, it can be achieved in tolerable combinations and is associated with improvements in overall survival in the context of several large randomized clinical trials.

The first presentation of a study from Palumbo and colleagues evaluating MPR-R (melphalan, prednisone, and lenalidomide for initial treatment, followed by continuous lenalidomide for maintenance) compared to

MPR and MD (melphalan and dexamethasone) further suggests that MPR-R may be another standard regimen. However, this concept needs additional follow-up.

Among patients who are eligible for transplant, the regimens with the most phase III data supporting their use include TD (thalidomide and dexamethasone), RD or dexamethasone, VD (bortezomib and dexamethasone), VTD (bortezomib, thalidomide, and dexamethasone), and PAD (bortezomib, doxorubicin, and dexamethasone). In this group of patients, we are seeing overall response rates of 70–100%. However, even more impressive is that the CR rates of 5–10% seen with VAD or TD increase up to 20–40% using novel agent combinations, and they increase even further in the post-transplant setting. With overall response rates approaching 100%, the new endpoints that we should be considering are more detailed assessments of CR, such as molecular or flow cytometric CR, and we should look more closely at the duration of CR. The latter is even more important among the group of high-risk myeloma patients, who we know may achieve CR quickly but may not stay in CR for very long with the use of conventional approaches such as high-dose therapy and autologous transplant alone. The initial dose of dexamethasone in combination with lenalidomide is still a matter of discussion, given the clear increase in toxicity in the high-dose dexamethasone arm from the E4A03 clinical trial, however it should be noted that this was less of a concern among younger MM patients than among the older MM patients, in whom high-dose dexamethasone was clearly not well tolerated. More importantly, the shift towards low-dose dexamethasone for all induction regimens has not yet been proven to be equally effective, and there are clear exceptions, such as patients who present with acute renal failure associated with myeloma, in whom the role of high-dose steroids can be critical to the goal of achieving rapid reversal of renal damage caused by light chain nephropathy.

However, the current developing question among physicians and patients is the role of maintenance therapy. Trials among older MM patients suggest that the progression-free survival (PFS) and CR rates are higher among patients who receive maintenance therapy with either VT (bortezomib and thalidomide), VP (bortezomib and prednisone), or lenalidomide; among younger post-

transplant MM patients, there are also data suggesting that lenalidomide may also improve PFS. Additional follow-up and more data are needed to answer this question of maintenance therapy, as one could argue that overall survival should be an appropriate endpoint in the maintenance setting or that perhaps age and cytogenetic profiles found with fluorescence in situ hybridization should play a role in this decision. For now, I think it is clear that the role of maintenance therapy is beginning to evolve, and the real question remains: For which patients is it of the most benefit?

H&O Does the standard of care differ according to different age groups?

SL Because of differences in tolerance of therapy, there is no single standard of care for newly diagnosed MM. For instance, for patients who are transplant ineligible, prednisone is better tolerated than high-dose dexamethasone. What is starting to be asked now is whether or not oral melphalan is necessary. Currently, a large randomized trial of over 1,000 patients is investigating newly diagnosed transplant-ineligible patients randomized to receive either RD or MPT in an effort to answer this question. This study is ongoing and has not yet been reported to date, but the question at its heart, “Can a non-melphalan-containing regimen offer similar or superior benefit as a melphalan-containing regimen?” is a critical one. Further to this question, Mateos and colleagues presented data in a plenary session at the 2009 annual meeting of the American Society of Hematology, where VTP was compared with MPV, and the question being asked was “What is the better partner for bortezomib?” The overall response rate for VTP was similar to MPV, but the toxicity associated with VTP was higher, suggesting that from an overall tolerance standpoint, melphalan was the superior partner for bortezomib in this population. However, with the availability of lenalidomide in combination with bortezomib, this may be a different story. I think that the elimination of melphalan at all phases is likely not the optimal solution, as in certain combinations such as with bortezomib, melphalan can be a very potent and powerful agent. However, questions about its use in all patients (high- and standard-risk) and about its necessity as part of a standard induction regimen among newly diagnosed patients still remain.

H&O What are some new agents that are being tested as potential options for frontline therapy?

SL New agents in development as part of induction include the expansion from 3-drug inductions such as VTD, VRD (bortezomib, lenalidomide, and dexa-

methasone), and CRD (cyclophosphamide, lenalidomide, and dexamethasone) to 4-drug inductions such as RVDD (lenalidomide, bortezomib, doxorubicin, dexamethasone) and CVRD (cyclophosphamide, bortezomib, lenalidomide, and dexamethasone). Data from several trials that evaluated these 4-drug inductions have been presented, but for now, their efficacy over 3-drug regimens is unclear. Additionally, the use of antibodies (eg, those for IL-6, CS1) and histone deacetylase (HDAC) inhibitors (eg, vorinostat [Zolinza, Merck], panobinostat [LBH589, Novartis], romidepsin [Istodax, Celgene]) is being explored in addition to the second-generation proteasome inhibitor carfilzomib (Onyx). Preliminary data on carfilzomib among patients who are bortezomib-exposed suggest that there may be a small cohort of patients who will respond to carfilzomib despite resistance to bortezomib, and among bortezomib-naïve patients, the overall response rate for carfilzomib is similar to bortezomib. However, in all reported settings to date, the incidence of peripheral neuropathy is significantly lower among the patients treated with carfilzomib. The IL-6 monoclonal antibody (CNTO 328) has been combined with bortezomib in a phase I/II trial and demonstrated superior time to progression when compared with historical data using bortezomib alone; the CS1 antibody elotuzumab (Bristol-Myers Squibb/PDL BioPharma), when combined with lenalidomide and dexamethasone, is demonstrating very high overall response rates (82% among all patients in the phase I/II trial), suggesting synergy for the addition of the immunomodulatory drug and a monoclonal antibody. Finally, the HDAC inhibitors, while not demonstrating any single agent activity in myeloma, are able to overcome bortezomib resistance in 30% of patients, suggesting that the combination of an HDAC inhibitor and bortezomib is clinically synergistic as well.

H&O What are some areas of research that are necessary to further understand the novel agents that are being studied for multiple myeloma?

SL In the induction setting for younger patients, the issues of importance include the timing of transplant and the role of maintenance therapy. Clearly, regimens such as VRD and VTD are able to induce very strong responses and a high rate of CR. For patients who achieve a CR, simply stopping therapy after 4 cycles is not a good option. If patients do not proceed directly to transplant, alternatives such as ongoing therapy or maintenance therapy are clearly needed, as 4 cycles of induction therapy are not sufficient.