

ADVANCES IN LLM

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

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Controversies Regarding the Use of Dexamethasone in Patients With Multiple Myeloma

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H&O What is role of steroids in the treatment of multiple myeloma?

SR Corticosteroids have been a long-standing component of myeloma therapy, for both newly diagnosed and relapsed/refractory disease. For a number of years, melphalan in combination with prednisone (MP) has been a standard therapy for the disease. In the 1980s, clinicians began using high-dose dexamethasone, particularly in nonalkylator combinations, such as with vincristine and adriamycin (VAD), increasingly as a pretransplantation induction therapy. High-dose dexamethasone was empirically chosen without any specific trial designed to determine the optimal dosage. Prior to the introduction of new drugs such as thalidomide (Thalomid, Celgene), regimens containing high-dose dexamethasone were preferentially used in patients who were candidates for transplantation; regimens containing low-dose steroids, such as MP, were used in elderly patients. Although corticosteroids reduce the level of monoclonal proteins and increase response rates in myeloma, their independent effect on overall survival has not been well established.

H&O Which patients were typically treated with high-dose dexamethasone historically?

SR In elderly patients, studies comparing dexamethasone versus prednisone did not show a survival advantage for high-dose dexamethasone. Therefore, newly diagnosed elderly patients who were not candidates for transplantation were not treated with regimens containing high-dose dexamethasone. On the other hand, younger patients

who were candidates for transplantation have traditionally been treated with regimens containing high-dose dexamethasone, such as VAD or thalidomide/dexamethasone. The paradigm changed with the availability of new drugs, and we began to ask whether there was a need to use high-dose dexamethasone given the availability of active, novel agents such as lenalidomide (Revlimid, Celgene) and bortezomib (Velcade, Millennium). The Eastern Cooperative Oncology Group (ECOG) trial E4A03 sought to answer this question.

H&O What were the findings of the ECOG trial and what is the role of dexamethasone today?

SR The main question when we designed the trial was whether we could achieve the same level of effectiveness with less toxicity by using a lower dose of dexamethasone (once weekly instead of 12 days monthly). The trial randomized 445 patients to receive high- or low-dose dexamethasone in combination with lenalidomide. We found that although responses tended to be higher with lenalidomide and high-dose dexamethasone, these responses did not translate into better overall survival. On the contrary, the low-dose regimen was associated with significantly better 1- and 2-year overall survival rates, as well as significantly lower toxicity. In the past, trials comparing MP versus melphalan and dexamethasone have shown no improvement in survival with the more steroid-intense regimen, but the significant survival advantage associated with the low-dose regimen in this ECOG trial was unexpected. I have reviewed the medical records of nearly all of the patients who have died on the study thus far in order to identify precisely what caused their deaths, and I have found that the excess deaths in the high-dose regimen are not explained by increased toxicity alone; rather, half of the excess deaths were due to toxicity and the other half due to myeloma. It is unknown whether the excess deaths in the high-dose arm due to myeloma are because of the fact that patients receiving

low-dose dexamethasone can tolerate the regimen for a longer period of time; because of significant side effects that debilitate patients and make them unable to tolerate a salvage regimen; or because of a true efficacy difference between the two regimens in the sense that high-dose dexamethasone somehow inhibits the immunomodulatory properties of lenalidomide. What is clear is that the increased rate of mortality with high-dose dexamethasone is not explained by safety differences alone. It is not due to prolonged therapy with high-dose steroids; almost all the excess deaths occurred in patients who received high-dose dexamethasone for less than 6 months.

H&O What were the toxicities seen in the ECOG E4A03 trial?

SR In the ECOG E4A03 trial, there was a significantly increased incidence of thromboembolic complications with high-dose dexamethasone. There was also a significantly increased risk of infection. The increased deaths due to toxicity were attributable to cardiac and thromboembolic events. Although ECOG E4A03 did not include a formal quality-of-life assessment, from the significant difference in grade 3 and 4 adverse effects between the two arms, it can be inferred that low-dose dexamethasone was associated with better quality of life.

H&O Was ECOG E4A03 the first trial in myeloma to demonstrate a lack of correlation between response and survival?

SR A reduction in the paraprotein levels is not a good surrogate for outcome in multiple myeloma, as has been shown in numerous trials. ECOG E4A03 was not the first trial to show a discordance between the arm with the higher response rate and the arm with the better outcome. For over 30 years, 25 randomized trials attempted to improve upon MP using various combination regimens, which typically provided superior response rates with no improvement in overall survival. Recently, there have been trials in both the transplant and the nontransplant settings showing that even complete response rates have not correlated with overall survival. The French trial in the transplant setting of melphalan, prednisone, and thalidomide (MPT) versus melphalan 100 mg/m² and transplantation showed that the latter therapy had a higher rate of complete response but significantly inferior overall survival compared to the three-drug MPT regimen. Another trial, from Arkansas, showed superior complete response rates with a thalidomide-containing regimen with no improvement in overall survival. Our goal should always be to try to improve survival, and in cases of equivalent survival, to try to improve quality of life.

H&O In what directions should research go as a result of these findings?

SR Researchers' first obligation is to prove that therapy works. With high-dose dexamethasone, we are faced with a therapeutic dose that was empirically chosen. Therefore, researchers are not trying to discard a proven regimen with a dose tested in well-designed trials. Over the last 30 years, high-dose dexamethasone has been in use mainly out of tradition and experience, rather than due to phase III data indicating that a high dose was necessary for superior survival. The ECOG study is the first assessment of two combination regimens that differ only in the dose of dexamethasone. It shows a survival advantage and reduced toxicity with the lower dose. Therefore, in my opinion, this trial finally settles the question of whether high doses of dexamethasone are actually necessary. High-dose dexamethasone does not improve survival and is thus unnecessary because of its side effects for patients with newly diagnosed myeloma. At best, no improvement in survival is seen, and, at worst, inferior survival is seen. As a result, in the future, research should not use high-dose dexamethasone as part of the regimens used to treat newly diagnosed multiple myeloma. High-dose dexamethasone has never been popular outside of the United States. European researchers typically use 4 days per month of dexamethasone. In the United States, both ECOG and the Southwest Oncology Group (SWOG), in their upcoming trials, have adopted a low-dose approach as part of their dexamethasone-containing combination regimens. Thus, thankfully, research has already moved away from high-dose therapy with this agent. In community oncology settings in the United States, high-dose dexamethasone has not been particularly popular, so it will be easy for oncologists to move away from this therapy. This new paradigm of low-dose therapy actually allows us to build on various regimens and create new ones that can be highly active.

H&O What agents are currently under investigation in combination with low-dose dexamethasone?

SR The combination of lenalidomide and low-dose dexamethasone has been shown to be extremely safe and effective, but researchers are still dissatisfied and want to improve upon this regimen. There are two cooperative-group trials that are going to test bortezomib plus lenalidomide and low-dose dexamethasone. SWOG is going to test lenalidomide and low-dose dexamethasone versus bortezomib plus lenalidomide and low-dose dexamethasone. ECOG is going to test bortezomib and low-dose dexamethasone versus bortezomib plus lenalidomide and low-dose dexamethasone. These two trials are trying to

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develop a three-drug nonalkylator-containing combination. There are ongoing US multicenter trials of four-drug combinations including cyclophosphamide, bortezomib, lenalidomide, and low-dose dexamethasone. In Europe, there are ongoing trials of cyclophosphamide, bortezomib, thalidomide, and low-dose dexamethasone. The goal of these multiple trials is to develop a regimen for newly diagnosed multiple myeloma equivalent to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for non-Hodgkin lymphoma.

H&O What is the status of research in the relapsed/refractory setting?

SR In patients with relapsed/refractory multiple myeloma, I do not believe the results from ECOG E4A03 fully apply. There may be patients for whom high-dose dexamethasone is needed. The regimen currently approved by the US Food and Drug Administration for relapsed/refractory multiple myeloma is lenalidomide and high-dose dexamethasone. I have seen a number of patients respond to higher doses of steroids when lower doses are no longer effective. High-dose dexamethasone alone or in combination continues to have a potential role in the relapsed/refractory setting.

Additionally, there are several new drugs in development for patients with relapsed/refractory disease, which

will improve the available treatment options. One such agent is the proteasome inhibitor carfilzomib (Proteolix), which has shown promising activity already. Another is CC4047 (Actimid, Celgene), another immunomodulatory thalidomide analog, which has shown activity in clinical trials.

Suggested Readings

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