Meet The Professors:

Oncologist and Nurse Investigators Consult on Challenging Cases of Actual Patients

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MULTIPLE MYELOMA

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DOSE AND SCHEDULE OF BORTEZOMIB IN MULTIPLE MYELOMA (MM)

MS ASNIS-ALIBOZEK: We received several questions about the dose and schedule of bortezomib for patients with multiple myeloma. Would you share your approach?

MS RICHARDS: At our center, particularly for a patient with high disease burden, hypercalcemia, renal insufficiency or a lot of bone disease we would administer bortezomib twice weekly for the first cycle. If the patient exhibits a good response, we would then switch to once-weekly dosing of bortezomib. We really try to switch to a once-weekly schedule, just because we've seen a lot less neuropathy since switching that schedule. Efficacy is also not compromised with the once-weekly schedule. On a study recently reported in which patients on one arm received once-weekly bortezomib while patients on a separate received twice-weekly bortezomib, the bortezomib weekly schedule exhibited similar efficacy with less neuropathy.

With regard to dosing schedule, we administer bortezomib once a week for four weeks and then we typically restage the patient during the week they're off and then restart bortezomib again. The bortezomib administration schedule also depends on what other additional chemotherapy drugs you may be administering along with bortezomib. For a patient receiving high-dose dexamethasone with cyclophosphamide, we would give them a week break and then restart bortezomib.

MS ASNIS-ALIBOZEK: Along the same lines, what bortezomib schedule do you utilize in regimens such as lenalidomide/bortezomib/dexamethasone (RVD), where you're combining an IMiD and bortezomib?

MS RICHARDS: A study by Dr Richardson and colleagues evaluated lenalidomide 25 milligrams up front on days one through 14 and bortezomib on days one, four, eight and 11. Studies have yet to be performed with a lot of these regimens actually on the once-weekly dosing schedule.

At our center, if we administer once-weekly bortezomib with lenalidomide, we administer just three weeks of the bortezomib, and then restart the next cycle with the lenalidomide on days one through 14.

It's really going to depend on which regimen you're talking about which other drugs you're combining with it.

DEXAMETHASONE DOSE AND SCHEDULE OPTIONS IN MM

MS ASNIS-ALIBOZEK: Several audience members also commented on the different doses and schedules for dexamethasone alone or in combination. Is there an optimum dose and schedule at which to administer dexamethasone?

MS RICHARDS: Again, you have to carefully evaluate each individual patient. If a patient presents with hypercalcemia and renal insufficiency, then it's really important to get a rapid reduction in the myeloma because that way you are helping to preserve and hopefully restore some of that kidney function. In those cases, we will utilize a high-dose dexamethasone regimen where we administer dexamethasone 40 milligrams on days one through four, nine through 12 and 17 through 20. If the patient shows improvement in their renal function and myeloma, then we will back off the dexamethasone after two courses, whereas patients on the ECOG trial, which evaluated once-weekly low-dose versus high-dose dexamethasone

received four courses of high-dose dexamethasone. We use dexamethasone for a much shorter duration than was evaluated in that study.

Now, when administering a bortezomib-based regimen, we will generally administer 40 milligrams dexamethasone day of and day after. When administering a lenalidomide-based regimen for a patient with no hypercalcemia or renal insufficiency, we will begin with low-dose dexamethasone. If they don't have response to the low-dose dexamethasone, then we would increase the dexamethasone to the high-dose level. Many regimens use different dosing schedules. We oftentimes refer back to the abstracts or the papers and evaluate the dosing schedules used and then tailor our dose and schedule for the patient.

CHOICE OF INITIAL THERAPY FOR PATIENTS WITH NEWLY DIAGNOSED MM

MS ASNIS-ALIBOZEK: Our next question was, which is the better regimen for patients with newly diagnosed multiple myeloma, bortezomib based or lenalidomide based?

MS RICHARDS: That's a difficult question to answer because at this point in time, there are no head-to-head comparisons. There hasn't been, for instance, a bortezomib/dexamethasone versus lenalidomide/dexamethasone study to really answer that question. There are some ongoing studies evaluating lenalidomide-based regimens versus bortezomib-based regimens. The issue is, however, usually it's a three-drug regimen versus a two-drug regimen. It's hard to know if the increased efficacy is because you're adding a third drug or if it's because one drug is better than the other drug. Still, it'll be interesting to see what some of the results show.

MS ASNIS-ALIBOZEK: Could you elaborate on how you are making those decisions in your practice?

MS RICHARDS: We evaluate each patient; we look at their comorbidities, and decide on a treatment based upon the patient. Oftentimes we do use a bortezomib-based regimen up front because there's not the difficulty with collection stem cells with bortezomib. Whereas with lenalidomide, after the patient has received more than four to six cycles, it becomes more difficult to collect stem cells, although that can be overcome with cyclophosphamide mobilization therapy.

Ideally, you want to get the patient to collection before four cycles, but obviously you don't want to compromise the transplant process just to get them in for collection at four cycles. So if they haven't had an adequate response, then you want to make sure that you've got that response before you send them for transplant. But again, there's not one best drug right now.

MS ASNIS-ALIBOZEK: How many cycles of bortezomib versus lenalidomide would you recommend prior to stem cell collection?

MS RICHARDS: We try and get the protein down as low as we can get it. We want at least a 50 percent reduction, but we know that the lower that we get the protein, the better the patient will fare with transplant.

If the patient receives two cycles and plateaus, then we would send them onto transplant. For some patients it takes two cycles. For others it takes four cycles. Again, you have to evaluate each patient and look at the type of response they have.

IMMEDIATE VERSUS DELAYED STEM CELL TRANSPLANTATION FOR MM

MS ASNIS-ALIBOZEK: A common question was whether patients should receive transplant up front or at disease relapse.

MS RICHARDS: I think if you ask differing centers, they would tell you different answers.

We perform transplant for the majority of our patients up front. We do have some patients that elect to go to transplant at first relapse. A study currently under way is comparing transplant up front versus at relapse. I believe that study will provide some useful information.

The difficulty in doing any studies in myeloma is that it takes so long to get answers because patients are living longer. We do not yet have an answer as to which approach is best with regard to overall survival.

One study which has been reported, which I believe was a retrospective analysis, evaluated transplant up front versus at relapse and there didn't appear to be a difference in overall survival, though there was a trend that the patients who received transplant at relapse had more skeletal-related events.

LENALIDOMIDE DOSING FOR PATIENTS WITH NEWLY DIAGNOSED MM AND RENAL INSUFFICIENCY

MS ASNIS-ALIBOZEK: The next question is as follows: If a patient receiving lenalidomide as initial therapy for MM develops renal issues requiring you to lower the dose, do you increase the dose of lenalidomide when or if the

creatinine clearance or renal function begins to improve? The caveat is, do you use lenalidomide in patients with a compromised renal function?

MS RICHARDS: In an untreated patient who has impaired renal function, we'll generally utilize a bortezomib-based regimen and not lenalidomide up front. For a patient who is refractory to bortezomib or one who experiences a lot neuropathy, we will use lenalidomide in patients with impaired creatinine, utilizing the dose reduction guidelines that are in the package insert.

If the patient's creatinine clearance improves, yes, we would increase the lenalidomide dose to the appropriate dose. I believe it's vitally important not to just be looking at the creatinine level but creatinine clearance as well. Because those dose reduction guidelines are based on creatinine clearance and not just creatinine levels. A patient could have an improvement in their creatinine level but not necessarily have a significant improvement in their creatinine clearance. It's really important to look at both factors.

REVERSIBILITY OF DISEASE-RELATED RENAL DYSFUNCTION

MS ASNIS-ALIBOZEK: One audience member specifically asked with regard to disease-related comorbidity and baseline renal dysfunction, once a patient is on dialysis, have you ever seen treatment for multiple myeloma allow them to come off of it?

MS RICHARDS: Yes. We've had patients who have come to us on dialysis prior to receiving any therapy for myeloma. Once we were able to get them into remission, they were able to come off dialysis. Usually, we use a bortezomib-based regimen because you don't have to worry about the renal dosing with bortezomib.

We have had a number of patients in whom we've been able to reverse kidney function, but the real determining factor as to whether the patient is going to be able to come off dialysis is how much damage there was to the kidney.

MAINTENANCE THERAPY IN TRANSPLANT-ELIGIBLE AND TRANSPLANT-INELIGIBLE MM

MS ASNIS-ALIBOZEK: Can you differentiate for our readers post-transplant and no-transplant maintenance therapy, and how many cycles are given before starting maintenance dosing in each of those settings?

MS RICHARDS: Most patients at our center go onto transplant. Generally, maintenance therapy is started three months post-transplant and it's dosed at initial dosing of 10 milligrams. If the patient tolerates that dose well, we increase it to 15 milligrams and they remain on that indefinitely.

The CALGB study in which patients were randomly assigned to lenalidomide or placebo reported that patients who received lenalidomide maintenance had a longer progression-free survival than those who received placebo.

For those patients who don't go on to transplant, once we see the myeloma levels start to plateau off, we'll generally continue the patient on maintenance. For instance, if we opt to administer lenalidomide and dexamethasone, we actually keep the patient on both drugs for about a year and then we'll back off on the dexamethasone and then see how they fare. If they fare well, then we'll decrease the lenalidomide dose from 25 mg to 15 mg, see how they do and then maintain them on that dose.

MS ASNIS-ALIBOZEK: We also received several inquiries about the use of bortezomib in the maintenance setting.

MS RICHARDS: If a patient received bortezomib as part of their induction regimen and subsequently did not receive transplant, we would administer bortezomib days one and eight every four weeks as maintenance therapy. We would use the same maintenance approach for a patient who experienced disease relapse while receiving a bortezomib-based regimen.

We try to back off the drugs one at a time to make sure that we know what drug was really a necessary ingredient to keep the patient in remission. Thus, if the patient was receiving a three-drug regimen, then for example we may back off on the lenalidomide and then we'll back off on the dexamethasone and then we'll start cutting back the bortezomib.

MS ASNIS-ALIBOZEK: And in the relapsed setting, after how many cycles do you start to back off?

MS RICHARDS: The approach is similar. When we see the myeloma plateau, that's when we'll start to back off. Now, in a patient who continues to benefit from treatment and they look like they could potentially go into a complete remission, then we will go two cycles past complete remission. In some cases we'll go on to maintenance, and sometimes, depending on the patient, we may actually follow them on observation and see how they fare. Sometimes you can follow those patients off therapy.

PROGNOSTIC ROLE OF CYTOGENETICS IN MM

MS ASNIS-ALIBOZEK: One audience member noted that in community practice, cytogenetics are not commonly performed. What are the implications for not using them and how do you use them?

MS RICHARDS: Cytogenetics are an excellent tool because they can assist us in identifying those patients who may have high-risk disease or a more aggressive disease — patients who have a translocation of 4:14, translocation of 14:16, deletion of chromosome 13 or deletion of 17p, generally have a more aggressive course.

Having this additional information also assists you in preparing the patient that their disease may not run the traditional course, not necessarily that you're going to tell the patient they are going to do horribly, but I think that you somewhat have to prepare patients that the disease is going to be a little bit more aggressive.

These patients generally go into remission very quickly, but then they also come out of remission very quickly. These are patients who definitely need to receive some sort of maintenance therapy once they go into remission. These are patients that probably will not have treatment-free intervals because their disease will just grow back very quickly.

MS ASNIS-ALIBOZEK: Could you also comment on the use of FISH and metaphase cytogenetics in your practice?

MS RICHARDS: Yes. We perform FISH analyses for those specific cytogenetic abnormalities on every patient.

MS ASNIS-ALIBOZEK: Do the results of cytogenetic testing alter the treatment course for your patients?

MS RICHARDS: We use a bortezomib-based regimen for most patients but, particularly in those patients who have the abnormal cytogenetics, we may use a bortezomib-based regimen. Also, we may use a combination bortezomib/lenalidomide regimen because bortezomib has demonstrated that it can overcome some of the genetic abnormalities except for deletion of 17p. Lenalidomide also has some data that show it can overcome abnormal cytogenetics, except for deletion of 17p. So a lot of times we'll use those drugs together to try and get the biggest bang.

BISPHOSPHONATE USE FOR MM

MS ASNIS-ALIBOZEK: Would you share your thoughts on the role of zoledronic acid in multiple myeloma in the absence of lytic lesions?

MS RICHARDS: We will administer zoledronic acid or pamidronate for patients who don't have lytic lesions, if they have, for example, osteoporosis. Even then we may only administer the agent every three-months. Otherwise the ASCO guidelines state that those patients who have lytic lesions should be placed on bisphosphonates. The guidelines are not clear-cut as far as approach for patients with osteopenia. Sometimes in those patients, we may place them on an oral bisphosphonate, such as alendronate or ibandronate, rather than placing them on the IV bisphosphonates.

PERSPECTIVE ON USE OF SUPPLEMENTS FOR PATIENTS WITH NEUROPATHY

MS ASNIS-ALIBOZEK: What approach is used at your institution with regard to the use of supplements for patients experiencing neuropathy?

MS RICHARDS: We don't use any supplements because we don't find that they work.

I know a lot of centers do use alpha lipoic acid, acetyl-L carnitine, vitamin B complex as prophylaxis to help prevent neuropathy. We haven't instituted that approach. When we've tried using those supplements in patients who already have neuropathy, we have found that very few patients benefit. Thus, we actually stopped using supplements and we instead administer pregabalin, gabapentin or duloxetine. We also use lidocaine patches to help manage neuropathy.

MONOCLONAL GAMMOPATHY OF UNKNOWN SIGNIFICANCE (MGUS)

MS ASNIS-ALIBOZEK: The last area of interest is MGUS. Can you explain a bit about what that is exactly?

MS RICHARDS: MGUS stands for monoclonal gammopathy of unknown significance, and what MGUS is is a blood disorder in which you have a cell that is producing this monoclonal protein, but it's not really causing any problems. The protein stays relatively stable and the cell never transforms, remaining in this benign state.

The thinking in myeloma is that most patients who have myeloma actually start off with an MGUS and then the cell takes another hit that results in transformation to a more malignant cell.

MS ASNIS-ALIBOZEK: What is the affect of having long-term MGUS on outcome if it ultimately progresses to myeloma?

MS RICHARDS: The risk of MGUS developing into myeloma is about one to two percent every year. So over a 20-year period, it's about 15 to 20 percent risk of developing myeloma.

An evaluation by Mayo Clinic of patients with MGUS stratified patients into different risk groups based upon their free light chain ratio and amount of M-protein. Patients with high-risk MGUS need to be more closely monitored for possible transformation to active myeloma, whereas those at low risk are likely to be fine.