Meet The Professors:

Oncologist and Nurse Investigators Consult on Challenging Cases of Actual Patients

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NON-HODGKIN'S LYMPHOMAS AND CHRONIC LYMPHOCYTIC LEUKEMIA

INTERVIEW OF AMY GOODRICH, CRNP-AC BY AVIVA ASNIS-ALIBOZEK, PA-C, MPAS

RITUXIMAB MAINTENANCE THERAPY IN FOLLICULAR LYMPHOMA (FL)

MS ASNIS-ALIBOZEK: We received a lot of questions about rituximab maintenance, and I wanted to ask you, what are your thoughts on dosing and how that affects toxicity?

MS GOODRICH: I believe it's important for nurses to understand that there is no standard for maintenance. The most commonly utilized schedule is weekly times four every six weeks, and most practices stop that after two years. There are schedules where patients get a dose every two or three months and then there are other groups that insist that you should be checking levels. When the rituximab level trends down to a certain level, then you should re-dose based on the patients clearance of the drug.

The biggest issue with toxicity is that of infections. Evidence shows that around two years, patients can become more prone to exotic infections as a result of the decreased number of B cells for an extended period of time — the immune system can only compensate for so long. For this reason, many practices typically discontinue maintenance therapy after two years.

The real take-home is that because B cells start to recover around six months, patients can react all over again each of those six-month time periods. So in terms of infusion events, nurses really do need to be on the alert.

MS ASNIS-ALIBOZEK: What do you typically do in terms of preventive treatment?

MS GOODRICH: We always premedicate patients with acetaminophen and diphenhydramine to try and prevent infusion events. If they do occur, we treat the patient symptomatically and use the most clinically appropriate drugs at that point.

MS ASNIS-ALIBOZEK: Many physicians inquired about the use of maintenance rituximab after rituximab-containing induction therapy. Would you say that's something you routinely administer?

MS GOODRICH: Yes. We have been doing it for quite a while now.

MS ASNIS-ALIBOZEK: Some of the audience members expressed concern about the development of resistance to maintenance rituximab. Do you share their hesitation?

MS GOODRICH: I think at this point it's a hypothetical risk. I am not aware of any data showing that that this is indeed happening, although a number of our collaborators are very concerned.

MS ASNIS-ALIBOZEK: If you had a concern about resistance, is that something you would discuss with your patients?

MS GOODRICH: At this point, there are not a lot of convincing clinical data that say there's an issue with resistance.

MS ASNIS-ALIBOZEK: Another question relates to patients who ultimately experience relapse. Will these patients, who have undergone long-term maintenance therapy, still respond to further rituximab treatment?

MS GOODRICH: In my experience, they tend not to respond well to rituximab monotherapy. There are data that indicate that once patients stop responding to single-agent rituximab, which is really what maintenance is, that adding it to further chemotherapy regimens continues to provide benefit for the patient — ie, more remissions, longer remissions and deeper remissions. However, if this is the case, it should translate into living longer, and so far it has not.

The take-home is that there is a possibility that maintenance rituximab could extend time until the next chemotherapy regimen. Most of these patients are focused on quality of life. They know they have a chronic disease and that they are not going to be cured.

MS ASNIS-ALIBOZEK: Next is a question about rituximab administration and CNS disorders. Can you shed any light on what is known about a possible association?

MS GOODRICH: There are some data that the risk of PML, or posterior multifocal leukoencephalopathy, is slightly higher in patients who receive more than two years of maintenance rituximab. The disorder, which is caused by reactivation of latent JC virus infection, is a progressive and rare disorder, potentially infection related and oftentimes fatal.

BENDAMUSTINE/RITUXIMAB (BR) VERSUS R-CHOP IN FL

MS ASNIS-ALIBOZEK: Can you explain for our readers how the efficacy and side effects of bendamustine/rituximab compare to those of R-CHOP in FL?

MS GOODRICH: 2010 data from Dr Rummel and colleagues reported that the time to next treatment was longer with BR than with R-CHOP, so the efficacy looks to be superior from that study and the side effect profile is certainly more attractive as well.

In addition, the infection rate is lower with bendamustine and rituximab. Patients get some mild hair thinning. There's no alopecia with bendamustine. For CHOP, people experience neuropathies because of the vincas, which is a much smaller issue with bendamustine.

The high-dose steroids with CHOP are eliminated with bendamustine as well. The only side effect with a little higher incidence is some dermatologic toxicity. But the big toxicities that you think of with CHOP — myelosuppression, infections, neurotoxicity, steroid issues and cardiac toxicities — these are the real issues in our older folks who may be diabetics and may have neuropathy from something else. These issues are significantly lower with bendamustine.

However, there is no role for bendamustine today in aggressive lymphomas, such as in diffuse large B-cell lymphomas. On the other hand, R-CHOP can be used as additional therapy to BR for follicular lymphomas.

Bendamustine is one more regimen in our toolbox, one more weapon in our arsenal. It is very efficacious and it's a little kinder and gentler than CHOP; although CHOP, I believe, will always have a place.

MS ASNIS-ALIBOZEK: We received a lot of case descriptions of patients with follicular lymphoma, asking about the use of BR. Do all of your patients with FL receive BR in the first line?

MS GOODRICH: We definitely have R-CHOP take a backseat in a large number of our patients. Now, if there's somebody that we're particularly worried about, such as if they have transformed disease, there hasn't been a proven role for bendamustine and rituximab in diffuse large B-cell and aggressive lymphomas. So we would choose R-CHOP for those patients. But in the vast majority of patients, we administer bendamustine/rituximab.

From a patient perspective and from a nursing perspective, as many practices have a triage nurse who manages all the toxicities, the side effect profile is better with bendamustine. From an office perspective, use of bendamustine eliminates a lot of the issues of patients in need of hydration or glucose checks. All these factors have an impact on the pace of clinical management.

USE OF RADIOIMMUNOTHERAPY IN FL

MS ASNIS-ALIBOZEK: Would you address the issue of incorporating radioimmunotherapy (RIT) into the treatment of non-Hodgkin's lymphoma (NHL)?

MS GOODRICH: We administer a fair amount of radioimmunotherapy here at Johns Hopkins, mainly because it's easy for us to do it. But there are barriers to using radioimmunotherapy. We have partners in nuclear medicine who are very interested in radioimmunotherapy and I believe that is really the key. As I go out and do talks, I find that for most clinicians who are not using RIT, the reason is because they have not forged those relationships outside medical oncology.

I believe that more radioimmunotherapy could and should be used. The barrier is that the medical oncologist is not independent in ordering it, administering it and then monitoring afterward.

MS ASNIS-ALIBOZEK: For what patient populations should one typically administer RIT?

MS GOODRICH: We tend to use RIT quite a bit in elderly patients with multiple comorbidities for whom we don't want to administer chemotherapy. We attempt to maximize nonchemotherapy options before jumping into chemotherapy of any sort.

We oftentimes administer RIT for patients who have experienced disease progression. Of course, many of those patients come from outside clinics and have received multiple lines of therapy. We also have a mechanism in place at Johns Hopkins in which such patients coming to us from an outside referral bypass medical oncology and go directly to nuclear medicine.

We do not administer a lot of consolidation radioimmunotherapy, mainly because we have so many other consolidation options via clinical trials. Although I'm well aware of the data and it's on the NCCN guidelines, I suspect that the RIT consolidation approach is only utilized in small pockets.

MS ASNIS-ALIBOZEK: Several audience members were curious about the side effects associated with this treatment. Could you elaborate?

MS GOODRICH: The most remarkable side effect is cytopenia. Patients become pancytopenic and begin to nadir at around four weeks and can last four to eight weeks. It's a very different nadir curve. In the clinical trials from which these drugs gained FDA approval, somewhere around 20 or 25 percent of patients needed platelet or red blood cell transfusions.

The recommendations are that patients get a CBC weekly for 12 weeks, so it's a little different from heme toxicity than we're used to. Otherwise, many of the side effects are very similar to radiation, in that patients can have a little bit of nausea and fatigue.

AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) IN NHL

MS ASNIS-ALIBOZEK: For our next question, would you explain which patients with NHL are considered for stem cell transplant?

MS GOODRICH: Everyone has a different philosophy about transplant in low-grade lymphomas because of the conflicting data about if autotransplantation is truly a curative option for these patients or whether you're just prolonging a remission. We give patients aggressive therapy as consolidation that's not myeloablative, so we don't rescue them with their own stem cells. Part of the dilemma is that there are lots of folks who have shown that you can still grow lymphoma from the stem cell product that you give back to patients.

So we know that many of these patients are being recontaminated with their disease, which is part of the dilemma of whether or not you should perform those transplants for follicular lymphoma. There are populations where this certainly is a very appropriate approach to consider. But again, many of these patients with NHL will be older, they will have comorbidities and they really may not even be candidates for autologous transplant.

MS ASNIS-ALIBOZEK: Could you also address the more aggressive lymphomas?

MS GOODRICH: The NCCN guidelines for mantle cell lymphoma (MCL) indicate that at first remission, patients should receive an autologous transplant, and that is definitely what we do here at Johns Hopkins. We try to place them on clinical trials as well, but transplants are definitely part of the backbone of MCL therapy.

For diffuse large B-cell lymphoma (DLBCL), the guidelines indicate that you should treat the patient, and then if the patient experiences disease relapse, administer salvage therapy and proceed to autotransplant. There are a number of available clinical trials which are trying to flesh out which patients are at the highest risk and in need of transplants and trying to get them to transplant before they experience disease relapse.

IMAGING MODALITY IN NHL: PET SCAN VERSUS CT

MS ASNIS-ALIBOZEK: We also fielded several questions about imaging. Is PET scan the preferred modality to follow tumor burden in NHL, rather than CT?

MS GOODRICH: PET scans are much more important in high-grade lymphomas than in low-grade lymphomas, although they're widely used in both settings. In my clinical practice, we tend not to do PET scans for patients with low-grade lymphomas. But that's very different in both MCL and DLBCL and other high-grade lymphomas, where if after initial therapy it looks like patients have residual, active disease, your approach is going to be more aggressive and you're going to take patients to transplant or you're going to administer salvage therapy. That's not the case in the vast majority of low-grade lymphomas.

The other issue is that some of these lymphomas are so slow-growing that they're not going to light up on the PET scan. So even though you get a negative PET scan, there could actually be active disease present.

PET is sort of a catch-22 because I also see patients coming to us from the outside who end up having reactive lymphadenopathy, and it's your immune system doing its normal job. So for practices where they do lots of these serial PET scans, they will be positive at times because things light up on PET scans other than lymphomas. Then you commit those patients to even tighter schedules of PET scans and biopsies for something that really may not have caught your eye had you just done a CAT scan.

FLUDARABINE/CYCLOPHOSPHAMIDE/RITUXIMAB (FCR) IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

MS ASNIS-ALIBOZEK: For our audience members inquiring about infection, what type of prophylaxis do you administer with front-line FCR for CLL?

MS GOODRICH: We administer PCP prophylaxis with either Bactrim or dapsone. We also administer viral and fungal prophylaxis, specifically agents like fluconazole, valacyclovir or acyclovir and Bactrim or dapsone.

MS ASNIS-ALIBOZEK: Could you also address the incidence of infection with that prophylaxis?

MS GOODRICH: You still see infections in those patients. But in front-line therapy, these patients tend to have a little more intact immune system. For patients beyond front-line therapy, you really need to be a little more diligent. Their cytopenias are going to be worse and their infection rates are going to be higher.

MS ASNIS-ALIBOZEK: Several physicians were interested in comparing FCR to FR in terms of infection. Are these two regimens at all similar?

MS GOODRICH: Cytopenias, infection rates and tolerance are very different. There are less infections and cytopenias, and FR is better tolerated. The addition of cyclophosphamide does make a difference.

MS ASNIS-ALIBOZEK: Another question was whether or not you incorporate cyclophosphamide.

MS GOODRICH: We are in a setting where we have a number of clinical trials and lots of options available for our patients. Since the average age for developing CLL is in the late sixties or early seventies, if you have an 85-year-old, you're going to think long and hard about administering FCR. But if you have a 30-year-old, you're going to be more inclined that they're going to tolerate it. We really do try to tailor therapy to the patient.

ROLE OF LENALIDOMIDE IN CLL

MS ASNIS-ALIBOZEK: One of the questions submitted was, is there a role for administering lenalidomide in patients with CLL?

MS GOODRICH: We use lenalidomide very sparingly in this setting because we have so many trials for patients.

We tend to use it after salvage therapy for patients who might have a very short remission. If their first remission only lasts six or nine months, then salvage therapy and using lenalidomide is a reasonable approach.

CHLORAMBUCIL AND ALEMTUZUMAB FOR CLL

MS ASNIS-ALIBOZEK: Finally, would you address the role of chlorambucil in the current treatment of CLL?

MS GOODRICH: Chlorambucil is approved for patients with fludarabine-refractory CLL. We also tend to use chlorambucil sparingly and mainly administer in elderly patients with comorbidities. I understand that on paper it continues to be almost the backbone of CLL therapy, but in practice, we now have other agents and kinder, gentler chemotherapy agents that are relatively well tolerated.

I actually prefer alemtuzumab, although some folks are wary to use it. We tend to administer it subcutaneously and not intravenously because it's better tolerated. The infusion reactions are less frequent with subcutaneous administration, although that observation is not widely proven and is more anecdotal. Again, this is an older population. Are these patients going to tolerate changes in their blood pressure and other issues that go along with all those infusion events? Also, although it is not widely reported, the infection risk is quite high.