Supplemental Faculty Insight
Questions and Answers

Q & A from Dr. Thomas Kipps' presentation

Q. ***Do high-dose steroids have any role in treatment of patients with CLL either in combination with an antibody or in combination with new kinase inhibitors?***

A. Actually, we have had very good success with the use of high-dose Solu-Medrol in combination with rituximab. It is a very effective regimen for depletion of B-cells and leukemic B-cells in particular. I think the important aspect that one has to always bear in mind with these treatments is the issue of immunosuppression after therapy. And with use of anti-CD20 antibodies in general, one can get worsening hypogamma-globulinemia. It is important to be vigilant for opportunistic infections, and perhaps have a low threshold for the use of intravenous immunoglobulins, particularly for those patients with hypogammaglobulinemia who develop recurrent or serious infections. We are actually now looking at the new third-generation anti CD20 which is obinutuzumab in combination with high-dose steroids and seeing particularly exciting activity. So, I think that the use of that regimen might be good for patients who may not be able to tolerate myelosuppressive regimens because it does seem to be myeloid sparing and generally well tolerated.

Q. ***How stable is ZAP-70 over the course of the disease in individual patients? Is the quality of the testing here in the US or Europe good enough to really use it on a broad scale? Is it justified in the patient who is maybe at an early stage of disease, indolent, and has no symptoms? Are the costs of this test and other tests you discussed justified?***

A. ZAP-70 can be challenging. Groups have tried to simplify the test. I know the group at the NIH with Jerry Marty and Adrian Wiestner has tried to look at different methods for measuring ZAP-70. Also working with Dr. Byrd, we have tried looking at methylation status of ZAP-70. In our hands, ZAP-70 has been very useful. I think that if you have difficulties in getting reliable data, obviously the use of that test is going to be challenging. It is almost like having a faulty watch though, if your watch is not working, you cannot ignore time. So, I think these tests do have value, but they have to be done in a fashion which is going to give reliable data. There is some discussion about changes of ZAP-70 over time, and this may perhaps be observed in some patients. We have not observed this generally, although I know that groups particularly in the Czech Republic and elsewhere have seen some changes in ZAP-70 that might occur perhaps in different microenvironments. So, I think like any test, we have to bear in mind that there are features that could complicate thing such as the quality of the test, the quality of the data, and as for cost, well I think this is a very important question to be debated overall. I do think the costs of any test have to be born in mind, particularly if the test gives rise to either treatment or further diagnostic tests that might either cause morbidity or mortality. So, I think that this is, as physicians, we have to be very careful about, but I do think some of these tests do have value for patients, particularly ones for newly

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diagnosed who want to have some outlook as to what they might anticipate. I myself, if I had CLL, would want to know whether I have a chance for more rapid disease progression than not, but I also say to patients that even though you have unmutated antibody genes or even though you have expression of ZAP-70, I have seen occasional patients that do extremely well over time. So, these are not guarantors of progression requiring therapy. And I think what is always important and what cannot be taken out of the equation is the quality of good medical management. So, you are the most important parameter in the management of your patient to observe the patient over time and monitor for changes or the acquisition of disease related symptoms or complication, that is our job.

Q & A from Dr. Peter Hillmen's presentation

Q. ***In the German FCR versus PR study, is there any difference in any data about secondary malignancies, and do we know anything about secondary malignancies with chlorambucil or obinutuzumab?***

A. Secondary malignancies are common in CLL, we see that certainly with skin cancers, obviously there is at least a double or more risk of getting skin cancers with CLL. I have yet to be convinced that there is any trial data that suggests an individual single therapy is associated with more solid secondary MDS and AML. I think continuous treatment or repeated treatment with the obinutuzumab therapies is likely to lead to more MDS and AML. And the question is, if you treat people at front-line who are appropriate for treatment, what is the risk in that group? Because I think it is the patients that have multiple lines of therapy who tend to have the MDS and AML as a problem. So, I do not think there is any evidence I am aware of that convinces me that therapy affects the solid malignancy rate, it might affect the hematologic malignancy rate, but maybe if we are treating people with good therapy front-line and then salvage them with novel therapies when they relapse, then we will not see such a big problem. I know that has been certainly a debate that Tom and I have had in the past where there is a greater fear of secondary myeloid malignancies because of the difficulty to treat those particular patients.

Q. ***In alternative treatment regimens for elderly non-fit patients, is there a role for bendamustine or the PCR regimen?***

A. The phase II data from a German group with bendamustine and rituximab looks interesting. You have seen the fit patient data. I think the data for BR in the phase II context for the elderly, there is not much elderly data actually, looks better than chlorambucil plus the antibodies, but there is very little data in an elderly comorbid population. There are trials ongoing, which I have one in the U.K. which compares chlorambucil/ofatumumab with bendamustine/ofatumumab plus or minus idelalisib. So, we will be gaining that data in front-line comorbid patients, but it is really hard to use phase III data to justify using BR and certainly not as good as FCR. For PCL, it is a very

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local use, I mean it is not widely used outside one or two areas of the world and I am not aware of any good comparative data to suggest it is as good as or better than FCR and no data in the elderly.

Q. ***In patients with autoimmune thrombocytopenia or anemia, would you consider using fludarabine or FCR in those patients and is there a role that maybe rituximab inhibits this autoimmune component?***

A. This will be an important question. First of all, I would separate the patients with hemolysis with those that have developed hemolysis on fludarabine as opposed to ones who have hemolysis without. So, I think it is a brave person, I have to note occasionally, who re-challenges patients with fludarabine who develop fludarabine-induced hemolysis. If you look at the randomized trials like the German trial and another trials, there is a low instance of elotuzumab hemolysis I believe with rituximab-containing regimes. And the patients with hemolysis, for example, who presented with hemolysis, I would control the hemolysis and then I am happy to treat with FCR if the patient needs treatment for their CLL, although sometimes they do not need treatment for their CLL. So, I think you can manage them if you treat with FCR drug a hemolytic episode which we sometimes have had to do, that can create a support problem for the first cycle of treatment, as the hemolysis is not switched off, so obviously that is a rare patient.

Q & A from Dr. Jennifer Brown's presentation

Q. ***How do we choose idelalisib over ibrutinib?***

A. I think lot of this is based on the toxicity profile and interactions. So, for patients who do require anticoagulation, I personally favor idelalisib over ibrutinib. I am still rather worried about using anticoagulation with ibrutinib, whereas those patients who have underlying hepatitis for example or underlying colitis, idelalisib could certainly be a problem for those patients and that would lead you to favor ibrutinib.

Q. ***In terms of a frontline treatment with these novel agents, can you say a little bit more about the use of idelalisib or ibrutinib in first-line treatment setting?****

A. Well, our data in the first-line treatment setting for these agents is still pretty limited. I did show some of the idelalisib upfront data and I do think the toxicity profile of idelalisib is rather more concerning in untreated patients than in relapsed patients. So, I think one would be hesitant about using it in that context. And even ibrutinib, we have only 31 upfront patients that have thus far been presented with the drug. Yes, but it has, so for 17p patients, although there is extremely limited, only one patient, I believe, who has been treated with 17p for upfront disease. Nonetheless, ibrutinib does have FDA approval for 17p frontline and I think that is because its relapse data is so much more impressive than any of our other options that we have for 17p patients. So, I think for 17p patients upfront, ibrutinib is a good choice.

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Q. ***How do you manage the patient's pneumonitis and colitis?***

A. As with any CLL patient, it is really important to do an evaluation for infection because I have found that there is often coexisting infection as well as potentially underlying drug effects. So, you do your usual evaluation for pneumonia including, for example, PCP or for colitis including C. diff, even in people who have not had antibiotics, and if you ruled infection and patients still have the ongoing symptoms, usually I hold drug at the time of the start of that evaluation, but they tend not to improve rapidly just with that, and so one can treat with prednisone for the pneumonitis, and I have had rapid resolution of pneumonitis in that setting. For the colitis, one can use prednisone, one can also use budesonide which is actually also quite effective and nonabsorbable, and so one can keep patients on that for some time and taper it off, sometimes with resolution and restarting or continuing drug. So, if you have decided you have a drug-related pneumonitis or colitis, you hold the idelalisib, at first suspicion of that I would say hold.

*****Idelalisib and ibrutinib are not approved by the US FDA for use in CLL

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