Q&A about Maintenance Therapy

Morgan Stout: Well, I know we have a lot of questions, we'll answer as many as we can. I'm going to ask one that was submitted multiple times in the registration is, **"What can a patient expect after maintenance?"**

Dr. Jonathan Wright: Sure. So for those in the non-muscle invasive bladder cancer setting, when we finish maintenance we just plan to continue with surveillance cystoscopies, and not giving anymore treatments. We just stop at the one year or three year depending on when it was. Then if there's a recurrence then we reset, and re-evaluate depending on the different nuances of stage, grade, timing, etc., but for non-muscle invasive just continue with the cystoscopies to monitor for a recurrence.

Dr. Petros Grivas: I think that the concept that Dr. Wright mentioned is important. Every time we give a therapy we want to see if it works, so we do diagnostic tests even when the cancer has spread in the metastatic setting. We do frequent CAT scans, and we may decide the frequency, how frequently to do it. The big question is what Gail mentioned before, how long we continue treatment, and that actually can be very relevant in different scenarios. The other point to mention is there's always important of a balanced discussion of benefits and risks, and we'll have to make sure we communicate that with the patient, and make decisions on an individual base on scenarios. When a treatment ... if the maintenance therapy, at least in metastatic disease based on this trial I showed you, usually the immunotherapy continues, again until major side effect happens, or the cancer grows again. However, in some cases people may stop at two years, and afterwards they do blood work, CAT scans just to keep an eye on things, we call this surveillance.

The last point I will make is ... because I saw a couple of comments or questions, people were asking what happens after they get what we call definitive treatment with an intent to cure the cancer, when the cancer is still localized in the bladder, and they can get either a radical cystectomy, meaning removal of the bladder, or they may get what we call a scraping of the bladder tumor, and then chemotherapy and radiation in attempt to keep the bladder. If there is no evidence of cancer after those curative intent therapies, we then just do surveillance, and what surveillance means blood work, CAT scans, exams, we do cystoscopies and urine analysis,(a cytology test for cancer cells), so this is a different concept, we call

this adjuvant. Sometimes we may use adjuvant chemotherapy if someone never received it before but this adjuvant discussion, which is what do you do when there's no evidence of cancer after removal of the bladder, it's a different question. Maybe another topic, Morgan and Stephanie, for our audience, especially in the context of new data coming out about the adjuvant postoperative setting.

Morgan Stout: Is it necessary to get the maintenance therapy after you've done induction therapy? Is it always or is there a situation in which patients would not get maintenance?

Dr. Jonathan Wright: I think that there's some nuances to it. I think in general if you meet the high risk criteria we're going to favor maintenance therapy, and same with intermediate, and have a discussion about the role of it. But it's very individualized with the patients, and if some had a very, very difficult time with the BCG, and in fact most of the failures from side effects in the studies happen during the maintenance time, sorry, the induction time, the first six weeks.

So they might just say, "Hey, when I'm weighing risks and benefits, it's just too hard on you." I think Joseph brought up a really big point too, and that is that some patients just can't travel, it's too big of a disruptor to their life, and not just an inconvenient, but just can't make that happen. You have to make a decision and say, "Okay, we're weighing the risks and benefits we're not going to be able to do it in this case." Then if it recurs we're going to treat it from there, but again this is just so ... again, it calls on the importance of having an open dialogue with your physicians to figure out what's the best thing to do for you as an individual.

Dr. Petros Grivas: From the more advanced disease perspective, I think that a practical answer is if someone starts with chemotherapy, and they achieve again a response or stable disease, and if there is no contraindication to immunotherapy I think it's a very reasonable option, and has definitely evidence that prolongs life. When I say contraindication, I alluded to a little bit during my talk, patients who have unrelated, not cancer, autoimmune condition like active lupus or rheumatoid arthritis, something that requires active steroids, it has to be discussed with the provider about the benefits and risks. Because many of those patients were not enrolled in this clinical trial, so there could be some exceptions, but for the time being we don't have any molecular marker, like a test we can do in the lab to select which patients may do better. So we use clinical criteria, especially those who achieve response or stable disease to the first line chemotherapy. Then if we're using immunotherapy from the get-go like with Gail, again we have a discussion of how long we continue.

Morgan Stout: Dr. Wright, you talked a lot about BCG today, is there maintenance with other types of intra-vesical therapies that we should know about, like gemcatibine/docetaxel or mitomycin?

Dr. Jonathan Wright: That's a great question, and I certainly focus with BCG because that is the preferred way to go for the high risk setting. There are certainly data supporting its role for chemotherapy as well, and when we have the BCG shortage that is affecting us, we have to do alternative treatments. So the data are quite as compelling for maintenance chemotherapy, but there are some data, I personally prefer if I have a high risk patient that can't get BCG to try to do a maintenance chemotherapy, but again it's a discussion. Some of my partners are less keen on doing it, again because it's just not quite as much of slam dunk, but I like the principle of the idea of maintenance. I think we're all trying to adapt and deal with the shortage of it. I think the short answer is,

yes, there are other alternatives doing chemotherapy for it, and when you're faced with a shortage you have to do those things.

Chemotherapy is going to work by killing an existing tumor, whereas immunotherapy might get what's starting to develop, so the biology might make a little more sense with the immunotherapy. But again, I feel like for my patients we talk about doing the maintenance chemo, that's the only option that we could get something before it's really ... when it's really small too. I think Joseph brought up an experience that his organization's been able to do, of splitting the dosage of the BCG in the setting of a shortage. The challenge is that a lot of patients won't have that available to them, because in a small practice when you split the dose you can't save it, you have to use it on that day. So you have to coordinate with another patient, or if you're doing third, two other patients to receive the dose or it's wasted. In a large organization that's Joseph's in they're able to do that, which is fantastic, but a lot of places won't have that opportunity available for them.

Morgan Stout: Absolutely, thanks. We had a couple of questions along this line: **"If you had induction therapy, and then for some reason didn't get maintenance, or if you were on maintenance for a little while and had to stop in both the advanced or the non-muscle invasive space, is there a protocol for a recurrence? Do you go through induction again?"**

Dr. Jonathan Wright: I can take it first. The non-muscle invasive, it depends. It depends if you have a small low grade, if you have a small grade recurrence which is low risk, we're just going to resect that tumor and go back to surveillance. If there was a high grade recurrence, if you had high grade T1 plus CIS, then we have to have a discussion, kind of how we started out the first time, BCG, chemotherapy, intra-vesical chemotherapy, or consideration of cystectomy. So I think it depends, we have to reset each time. There's also some nuances to how long it's been since you last received BCG, we can do it again. So there's not one set answer, again it's the dialogue, taking everything into consideration, and finding the right treatment for you.

Dr. Petros Grivas: I think the same principles apply to the metastatic disease setting, it depends on the timing sometimes. For example, if some patient finishes chemotherapy and then goes on to the immunotherapy maintenance, the timing is important when this cancer starts growing again. Is it within a few months, or it's years later? The other parameter is how well the patient tolerated the chemotherapy, the induction phase, and its side effects. Did they do okay or they struggled with it? These parameters come to play, and now we have a good news, we have new treatments that are becoming available and FDA approved, what we call antibody-drug conjugates, other drugs that are for target therapies. There are two other drugs approved by the FDA for patients who have progression on prior, the cancer progression I mean, prior chemotherapy and immunotherapy, things like enfortumab vedotin or dasatinib, FDA approved agents. All those doing many clinical trials to try to create more options, and try to help our patients live longer and better.

Morgan Stout: Absolutely. Thanks. I just have one more question, and it's actually for our patient advocates, **"If there was one thing you would suggest that the folks on this program talk to their doctors about maintenance therapy, what's the one thing you would tell them?"**

Joseph King: I would talk to the doctor about the availability of BCG. I would ask him also which type of schedule I'll be on, and the really important one us to be your own advocate. Because originally they told me, "You're going to only get two and a half years of the BCG," and I said, "Wait, I have CIS." CIS changes everything, that's the changer, and so they told me now three years.

Now, because I have a recurrence I'm not sure. Dr. Wright gave me some good information this morning. I'm not sure what they'll do, but I think the big thing is that throughout the bladder cancer experience I have told people over and over again, because I'm now a survivor-survivor, treated like a little counselor, to get second opinions frequently if the doctor is not serving your needs, please, to ask another doctor. You can't get BCG from one, go somewhere else, and so you have to be your own advocate, that I would say that that was one of the things that I really ... My first doctor offered no BCG so I went to a new one, another one, so that's what I would say for me.

Gail Dykstra: I want to echo what Joseph just said about being your own advocate. I think that that's very important, and that you need to find a treatment center that is going to not only respect that, but anticipate that with additional data so that you always know that you have options, that you have continued information. Because this isn't just a one-time decision, in a maintenance treatment phase you're making a decision on a regular basis because you're being examined on a regular basis. The what if question, what now question is always going to be in your mind, and so by having that kind of open and frank communication, and knowing that you are getting the kind of respectful treatment, and the latest data is absolutely essential.

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