The Practical Oncologist

New Essentials in Practice for the Treatment and Management of Advanced Melanoma - Part 2

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Flaherty: Thank you Dr. Kirkwood. It is my pleasure now to present you with several case studies where I will incorporate and put into practice the information we have just heard from Dr. Kirkwood. Following each case presentation, Dr. Kirkwood and I will have a short discussion regarding the challenges and treatment decisions impacting the outcome of the case.

Let us start off with a 62-year-old man with a primary melanoma on the right arm. An excisional biopsy reveals a 4.5 mm thick melanoma with ulceration. Clinical examination reveals a palpable lymph node in the right axilla. Staging CT scans reveal no other evidence of disease. An axillary lymph node dissection reveals melanoma in the enlarged lymph node and microscopic involvement of two additional nodes. In summary, this gentleman has a T4N1b melanoma. Resected in 2005, he subsequently was advised to consider high-dose adjuvant interferon, which he received. In 2009, he presents with a palpable right supraclavicular lymph node. A fine needle aspirate was performed and reveals evidence of melanoma. Staging CT scans revealed several enlarged right axillary and mediastinal lymph nodes, lung, and liver lesions. A serum LDH was sent and it was found to be two times the upper limit of normal. A tumor block from the 2005 lymphadenectomy was requested for BRAF mutation testing and in this case, the most common BRAF mutation, the V600E mutation was found. On these images you can see here, evidence of the right axillary adenopathy.

Dr. Kirkwood, what I would like to discuss in this patient who has a fairly extensive disease burden and elevated LDH, but not necessarily compromised with symptoms, what our treatment considerations might be.

Kirkwood: So, I think as we have just reviewed the options for interleukin-2 now for ipilimumab, would be attractive, but I think given the elevated LDH, given the burden of disease, this is a candidate for more rapid intervention, rapid results with the BRAF inhibitors given the presence of a mutation V600E.

Flaherty: I think you highlight a couple of points there. One of course is that for a patient like this, we do have multiple treatment options and in trying to discern the best, we are a little bit limited by the data in the sense that we do not have sort of the comparative type of head-to-head analysis that would give us a sense of what the best first therapy is or best sequence, but clearly, vemurafenib is an agent that had shown activity and a survival advantage in patients just like this. Not to say that ipilimumab cannot work in such a patient, but I agree with you, thinking about this particular patient's presentation, while some might consider it a borderline call, probably favors in the direction of starting with vemurafenib. In my view, I would be interested in your perspective, I think a case like this in some ways can be decided on the presence or absence of disease-related symptoms, with symptoms being a very strong endorsing feature for choosing the BRAF inhibitor approach and whereas an asymptomatic patient with excellent performance status, perhaps even with this disease burden, you might think about ipilimumab first time.

Kirkwood: Exactly. But I think the symptom complex is the defining factor that propels us toward the targeted therapies in this particular case. I think in the absence of symptoms or in the absence of disease, which we would presume might cause symptoms for this patient where we had perhaps 2 or 3 months that we thought we could use to either test the benefit of interleukin-2 or of ipilimumab, we would consider the BRAF inhibitor.

Flaherty: Agreed. So, with that, let us maybe try to shift the discussion a little bit with another case.

Here is a younger patient, 47-year-old woman with a T2N1a melanoma resected in 2004. The primary tumor was on the right leg and a single positive sentinel lymph node had been identified at that time. The patient had been counseled about her adjuvant therapy options and declined adjuvant interferon. In 2010, she presents with a pigmented cutaneous lesion on the right leg. In fact, several were identified. Staging CT scans were performed and revealed deep right inguinal and right pelvic lymphadenopathy. Her serum LDH though was normal. One of the cutaneous lesions was biopsied and BRAF mutation testing was performed, and once again the most common BRAF mutation V600E was found. Radiographic studies demonstrate the adenopathy. Sufficiently well developed, particularly in the pelvis, to make this patient deemed to be unresectable by a surgical oncologist, and so immediately now the discussion shifts to the notion of systemic therapy.

So, what do you think in this situation Dr. Kirkwood? Here we have a significantly lesser burden of disease, so-called M1a disease by the AJCC designation, and the patient is not burdened by the disease we presume in terms of symptoms. So, thinking about this patient, again, multiple treatment options, how do you think through the treatment armamentarium for her?

Kirkwood: So I think the patient here is a young patient. I think that always gives us greater confidence to pursue more aggressive therapies, potentially more toxic therapies, and in particular interleukin-2 and ipilimumab in those categories. I think the fact that she has normal LDH, the fact that she is asymptomatic, the fact that this disease is in lymphatic basins where the immune response clearly has failed to cope with it, but where the immunopotentiators, interleukin-2, ipilimumab, both that should benefit, I think we would certainly consider this patient for IL-2. If she would not come into the hospital and decide it on the basis of a requirement for hospitalization to deliver IL-2, we would certainly consider ipilimumab for her.

Flaherty: Right. I tend to agree. This is exactly the kind of situation where while interleukin-2 does not have a fool-proof track record in terms of efficacy, one would consider this patient has the time to receive that therapy, obviously aiming for response, but if she does not respond, she has got time to fail, if you will, and still have treatment options thereafter. The key feature of the data that you presented previously, true for both vemurafenib and ipilimumab, is there is very clear evidence of efficacy even in patients who have had interleukin-2 previously and not responded. So, I think it safe to say you do not really burn a bridge with that approach as a first line of treatment and obviously durable response with that is a feature. Also for ipilimumab so as you said the patient ultimately holds the cards there, but it is also possible, of course, depending on how the disease course were to go that even if she did progress on interleukin-2, you might still be in a situation where another immunotherapy could be considered even in this patient where you have got the knowledge that she harbors a BRAF mutation. Again, this is going to be an issue where we need ongoing clinical trials in my view to try to address this optimal sequence point, but I think based on available evidence, interleukin-2 first and then re-address if needed on disease progression.

Kirkwood: I think as you pointed out Keith, the fact that after a couple of cycles of interleukin-2, after say 6 weeks, we would know to a greater confidence to an 80% to 90% confidence whether she was going to be responsive says that is perhaps the quickest track of an immunotherapy to knowing that she would be the beneficiary of that and if she did not, we would certainly consider ipi to follow that, but whether to lead off with the one or the other I think is at this point unsettled dealer's choice.

Flaherty: And for the practitioners who themselves do not give very much interleukin-2 but maybe have a physician in their area referral center they consider, in 2012, how would you describe your sort of the thresholds or the demographic features and disease features that in your mind still identify an IL-2 candidate?

Kirkwood: Well, because IL-2 is given as an in-hospital treatment, we actually have patients who come to Pittsburgh from Canada, from all regions. The treatment is a confined 4-day interval in the hospital. The patient then returns home and back to their

work, so I think the demographics are a little less constrained, although you are absolutely right, it is not every hospital that does this therapy. I think as we also know the support of ipilimumab therapy requires specialized knowledge, experience, I think that also needs to be factored into the equation and there may not always be people who would know and be confident to administer this, but again if they are not, I think the regional centers that can administer ipi should be pursued.

Flaherty: Let us again go back to this issue about thinking through optimal treatment options with another case.

So here again, a young patient, 35-year-old man, with a T3N3 melanoma resected in January 2011. Primary tumor was on the chest wall. The patient was eligible and enrolled on a MAGE-3 vaccine adjuvant trial, but unfortunately, in May 2011 presents with ipsilateral supraclavicular adenopathy. Staging CT scans reveal innumerable lung metastases, 10 liver lesions, the largest being 3 cm, bilateral adrenal metastasis, and a serum LDH in this case that is 4 times the upper limit of normal. One of the previously resected lymph nodes was sent for BRAF mutation testing and yet again a V600E BRAF mutation was present.

Dr. Kirkwood, just so you do not think I have completely stacked the deck, these BRAF mutant cases if you will are just to try to really focus in on this treatment algorithm for those with the most treatments, clearly for patient who lack a BRAF mutation, we shift the discussion, but we can come back to that in a little bit.

So, here is a patient with significantly more disease burden. The radiographic study showed very clearly fairly heavy involvement of the liver and while liver function in this instance is not yet imminently threatened, it would not be in the too distant future with more disease progression where one would expect that.

So again, now thinking about this other extreme if you will of presentation, the patient had a high burden of disease if you will when initially resected, very short interval in terms of relapse, now symptomatic multi-organ involvement. So, what are you thinking here in light of the available evidence?

Kirkwood: I think we owe our patients, both the maximization of symptoms, symptom control, and the maximum opportunity to have survival benefits from therapy. In this particular case, the gentleman is symptomatic. The fact that he is symptomatic pushes us a bit further a bit more even than the first case does to consider the rapid return that we have from the BRAF inhibitors. I think this would be a case that we would think first and second and may be third about the BRAF inhibitors, and it does not mean that the patient would not or could not respond to interleukin-2 or ipilimumab, but I think the time window that we would like to have, even if it were 6 weeks for the interleukin-2, a couple or 3 months for the ipilimumab, is something that we would

rather rapidly remit his disease. Ultimately, this would be the potential person for a combination approach of BRAF inhibitor followed by IL-2 or ipilimumab as we have talked about.

Flaherty: Right. I think there is obviously a temptation already with multiple agents FDA approved currently to think about the idea of mixing them, particularly in a patient like this who is in somewhat crisis mode, but I think as you have highlighted in your presentation previously, this is still really a question where we first have to address the safety and make sure that the therapies actually do not interfere with one another, cannot really assume just yet that they are efficacious in combination, but I agree with you, until we have more information, is going to be single-agent vemurafenib for a patient like this and then after improvement in symptoms and disease burden, watch the patient very closely with the idea that perhaps there might be a window to think about moving to a second-line immunotherapy.

Great. Well. I did want to introduce one other case because I think it highlights another key point about the new therapies that you touched upon in your presentation.

Here is a 54-year-old man with a 2-mm thick melanoma, at least Clark level 4, non-ulcerated, 4 mitosis per square millimeter, identified on the scalp. In terms of regional disease, two palpable lymph nodes were detected on physical examination and upon lymphadenectomy, a total of 10 out of 77 neck lymph nodes were found to be positive for melanoma. So this is a patient with AJCC stage IIIC disease, quite concerning in terms of subsequent risk of recurrence and was counseled about the risk of recurrence and the adjuvant therapy options, elected to receive one year of high-dose interferon. In January of 2011, the patient presents with a seizure. A brain MRI reveals two dominant brain metastases and several smaller ones. A tumor block from the 2010 lymphadenectomy was requested for BRAF mutation testing and once again here, the BRAF mutation was found. The radiographic studies demonstrate the two larger brain lesions with surrounding edema and now, in this patient who has got brain predominant disease, it would appear based on the complete staging analysis has a BRAF inhibitor option because of the presence of mutation. How would you think through decision making in terms of patients with brain metastasis in general? And we can use this case as a starting point for discussion.

Kirkwood: In this particularly patient, we know from the tempo of his disease that this is not likely anything but melanoma in his brain. I think for the patient who can present with the same kind of picture remote from a melanoma or without a known primary, craniotomy obviously would be the consideration for diagnosis and even for management of solitary lesions. This patient has two on contralateral sites of the midline, it would be very difficult to think about surgery benefiting him alone and I think stereotactic radiosurgery up until the past year would have been a clear consideration. One that I think we could predict with solid assurance would benefit the patient 70% to

80% of the time, although not always for as long as we would like, but I think in the last year since the demonstration that Georgina Long presented to ESMO of BRAF inhibitors showing activity in patients with central nervous system metastasis from melanoma be really exciting hope and one that I mentioned in the course of my discussion has now been tested in the phase 2 trial but we can hope to hear about at ASCO where the benefit as intonated by Georgina Long might have been or might be even 80% of patients who can benefit, I think 50% is what we see in the extracranial sites, it is very likely that at least 50% will be the benefit rate we can anticipate from BRAF inhibitor therapy for CNS metastatic disease.

Flaherty: Right. Well, could you revisit the issue of ipilimumab efficacy in the brain? Let us take this case but perhaps reduce the tumor burden in the brain a little bit, maybe have several small brain metastases. I guess the question that comes up is if the emerging evidence would suggest that the BRAF inhibitor can be effective in the brain, as well as elsewhere, how about ipilimumab?

Kirkwood: Well, there is clearly also evidence there presented even a year earlier to ESMO that suggests that the ipilimumab effects are also seen in CNS metastatic disease, the ultimate response rate seen in the BRAF inhibitor interventions compared to the ipilimumab require a little bit more time to know, but I think both of these are clearly modalities available to the patient with CNS metastatic disease.

Flaherty: I think in my practice now, I would say at least for relatively small burden of disease in the brain, I would say we can have probably just enough confidence to say that we almost do not need to account so much for the presence of the brain metastasis, at least in choosing between these two systemic therapy options. Of course, we have known for quite some time that high-dose interleukin-2 is probably not a great choice in patients who have brain metastases, particularly if they are large enough to have surrounding edema for fear that the interleukin-2 in fact could increase that inflammation. I wanted to get your thoughts regarding some of the special considerations as we have considered these cases whether they be better candidates for vemurafenib or ipilimumab in terms of some the toxicity considerations. So I think that in your presentation you highlighted a few of the key points, but as you put ipilimumab into practice, how do you counsel your patients in terms of what to look out for, what to contact you for, and then just at least a couple of the more common scenarios you have to wrestle with in terms of management.

Kirkwood: Sure. Well, as we discussed in the didactic session of this, I think the four systems that we really need to think about in every patient being treated with ipilimumab are the skin, the endocrine organs, the liver, and the gut. I think clearly the rash that we see more commonly with ipilimumab is generally easily managed, but a couple of percent of patients may have Stevens-Johnson, toxic epidermal necrolysis, bullous disease, those need to be considered. Clearly the endocrinopathies seen in a

number of patients with this intervention, thyroid, adrenal, hypophysitis, things that we need to be all on our toes in our medicine in our endocrinology to manage need to be also on the front burner as we are thinking about patients followed on this modality. The hepatic enzymes we are going to follow we will know that it is not usually so much of a secret if hepatitis is going to occur, and symptomatic but oftenly ignored too long colitis, inflammatory bowel disease, precipitated by this as an immune-related adverse event is a major cause of concern, 7% of grade 3 to 5 incident cases of colitis in the pivotal study, and I think that, more than anything requires anticipatory preparation, the physician who manages these patients needs to be in continuous dialogue with patient. It is unacceptable for patients not to feel able to report bowel habit regularly, and with that I think we all hope that we can manage this expectantly without some of the calamities that have befallen patients in the phase 3 studies and in practice when this is not heeded.

Flaherty: I think your point is well-taken in terms of this window of observation. It extends over the course of the induction therapy, the four planned doses, and even perhaps a little longer still in at least several weeks thereafter where patients need to understand they need to have a very low threshold for reporting skin changes, changes in bowel habits, or generally feeling poorly, frankly, that is beyond what they were experiencing a day or two before as any of those could be monikers of an immune effect that needs to be addressed and I think it is frankly very difficult to give patients very much pre-instruction about levels of concern and so on. I think that really needs to be the physician who judges that and just with a reliable dependence on the patient to report of these findings. So I guess one question in real-world practice, how frequently do you face a situation where you either have to discontinue the ipilimumab or institute corticosteroids? I mean this sort of showstoppers of sorts in terms of ipilimumab-related toxicities.

Kirkwood: I mean, I think the different dosages of 3 mg and 10 mg that we are studying in the national trials appear to have different rates of toxicity and I think we need to be prepared to use and probably to use a bit more of the steroid interventions that should not be reserved just for the patients who come in with already established grade 3 colitis.

Flaherty: Right. I agree. This issue about finding exactly what that trigger point is is still a learning curve a bit in the field, even with the drug having been in clinical trials for more than a decade at this point. Well, I wanted to make a few comments about vemurafenib and certainly get your thoughts. A couple of key points as we talked about in the case series there was that this is really only a therapy that you can consider once you have got the BRAF mutation result in hand. Thankfully, in real-world clinical practice, that result can be generated fairly quickly, so that does not seem to be the limitation, but just to reiterate the key point that we really do not have a basis for thinking that a BRAF inhibitor approach could be plausibly useful in patients

who do not have a BRAF mutation. In terms of some of the unique downsides, I would say a general take-home point from your presentation is that the side effects are generally not serious, although they can be bothersome in some cases, and if they do interfere with quality of life or in the case of some of the laboratory abnormalities like the transaminitis if they are sufficiently elevated, usually holding the therapy results in relatively quick resolution in symptoms. And generally patients can restart treatment, although depending on the severity, may need to start at a lower dose initially. The key observation from the early clinical trials and all the way through with the emergence of these squamous cell carcinomas of the skin were also sometimes identified as keratoacanthomas related entity certainly was a cause of concern that a treatment like this could result in the appearance of an unrelated malignancy, although at least in my experience and to my knowledge, there have not been clear instances of any other cancer types emerging on therapy, so obviously something that we in the field need to keep a steady eye on as we continue to monitor the use of these therapies in practice. But my feeling is at least based on what we know now, these cutaneous lesions can be excised and patients could continue on therapy. I wonder if you have thoughts in terms of the other issues that might force you to interrupt therapy?

Kirkwood: I think your point that one needs to have documented V600E or K mutations to feel comfortable to apply this therapy critical because in the absence of this in the wild-type setting, the disease may actually even be accelerated by the use of the BRAF inhibitors, so I think this is a therapy that needs to be guided by that molecular genetic testing. I think that the toxicities that we have seen, the arthralgias, the dermatopathy, are often considerable, even the photosensitivity is sometimes a showstopper for patients who have their lives out of doors and even between the cancer center and their vehicle get a burn that is quite severe on these photosensitizers. But I think all told, your point is also well taken that these are relatively less concerning than the toxicity of the immune-related delayed and often not at all acute toxicities that we see with ipilimumab, when we use interleukin-2, patients have their toxicities right in front of us, we are going to know all of those in the hospital, be able to support them and when they go home, we do not usually have issues to deal with. Ipilimumab is the therapy where we need to be in continuous touch with the patient. They need to have access to us, to our staff, so that there is no question that there is communication for support to optimize this therapy, but I think with that, this is a whole new era, I think this is a whole new ballgame, I think this is one where the combinations as you pointed out will be of even greater hope for the future.

Flaherty: Thank you. In closing, I would like to thank Dr. Kirkwood for his participation in this program and thank you for joining me.