

## **Round Table Case Discussions, Part 1: Debatable Role for Radiation, and Value of Maintenance Therapy with Drs. Julie Brahmer & Gregory Riely**

Dr. West: I'd like to welcome my two guests, who are kind enough to spend time talking about some interesting challenging cases with us. They are Dr. Julie Brahmer, who is an Assistant Professor in Medical Oncology and a lung cancer specialist and expert at the Sidney Kimmel Cancer Center at Johns Hopkins University in Baltimore; also joining us is Dr. Greg Riely, who is an Assistant Professor in Medical Oncology and also focusing on lung cancer at Memorial Sloan Kettering Cancer Center in New York, New York.

I'm Jack West, medical oncologist at Swedish Cancer Institute in Seattle, Washington. I'm also the President and CEO of GRACE, the Global Resource for Advancing Cancer Education. What we'll be covering today are three cases that I think will be quite thought-provoking and that illustrate interesting challenges that we face sometimes even when patients do unusually well. With that, I'm going to move to the first case.

The first case is a 63-year old woman who doesn't have any significant past medical history. She developed an increasing dry cough in July of last year (2009). At the same time, she was also developing some night sweats with temperatures in the low-grade 100° - 101° F. She has a prior smoking history. She'd quit smoking in 2002 and she had previously smoked a pack per day for about 40 years. She saw her primary physician who did an x-ray that showed a large left lung mass. This was followed by a chest CT that revealed a nearly 8 centimeter left upper lobe mass that was adjacent to the aorta arch and we'll see some images of that. She also had some bulky subcarinal and right as well left hilar lymphadenopathy which is what the LAN stands for. That led to her being sent to a pulmonologist who on exam noted a 2 cm firm lymph node in the lower part of the neck on the right side. This was on the opposite side of her main cancer.

These are some of the images from her initial scan. This primary mass is on the left side. It's obviously pretty large. This is the top of the aorta arch; so it's right along there. In the lower panels you can see some of these gray areas represent soft tissue basically lymph nodes that should not be so large and are abnormal.

She ended up having a bronchoscopy by the pulmonologist who did her evaluation. That showed a poorly differentiated non-small cell lung cancer. The histology came back as "not otherwise specified". It's important to distinguish that sometimes we see this answer because there isn't enough tissue available to make a clear answer. Sometimes we get an answer back of, "we can't really characterize the subtype of lung cancer such as adeno or squamous or another because there's a tiny amount of tissue available. If we had a bigger biopsy it would be more feasible."

She had a head MRI that showed no brain metastases -- looked okay. She had a PET/CT scan that showed the left upper lobe mass with a high amount of uptake,

an SUV, or standard uptake value, of about 16 which is pretty unambiguous for cancer involvement; as well as elevation in the metabolic activity of multiple areas of lymph node involvement on both sides of her mid-chest, the mediastinum; and also on the right side of the upper part of her right chest and in a neck node on the right side.

So she had actually seen an outside radiation oncologist who reviewed her imaging and the overall clinical situation and did not feel that radiation was a feasible option at that time but did say it might be an option in the future depending on her response to any treatment that she might receive.

Perhaps the leading question I would start with, this is a case where the radiation oncologist has actually seen the patient and says that radiation is really not feasible, but this would be prohibitively large as a radiation field and too toxic to give with concurrent chemotherapy. There are other settings perhaps that are more ambiguous such as N3 nodal disease which is pretty locally advanced even with lymph node involvement on the other side above the clavicle, or supraclavicular region. I'd start with asking perhaps Dr. Brahmer first, when you see a patient such as this is your approach going to be consideration of a multimodality curative approach or is it really when you see contralateral, or opposite side, supraclavicular nodes involved that this is somebody who you're trying to prolong survival and do well in terms of symptoms; but is not something that you could approach with a curative strategy?

Dr. Brahmer: Certainly this does happen, and in this case the extent of the adenopathy with the lymph nodes is extremely concerning and the likelihood of cancer elsewhere even if probably microscopic is quite high. Usually in this situation it would be very difficult to give radiation therapy and chemo for a curative intent. The likelihood of cure would be quite low. In some patients who have a very small amount of lymph nodes on the opposite side involved, such as the supraclavicular lymph node, we try to err on the side of giving the patient the potential benefit of cure and so we will try to do chemotherapy and radiation. But again, those patients are patients who have not lost any weight, no other systemic symptoms that I would feel comfortable trying to do that. It isn't without cost: the radiation side effects would be quite high because you'd have to include such a large amount of normal tissue within the radiation field. We would try if it was just one lymph node on the contralateral side. But if there's multiple lymph nodes, it's extremely difficult.

Dr. West: Greg, what would your approach be or do you have any kind of standard at Memorial for someone who is really on the outer reaches of what could be feasibly considered for cure, but is outside what would commonly be included in say a cooperative group trial?

Dr. Riely: I think this particular case raises a couple of issues in my mind. One that struck me at first is, as we evaluate a patient initially, we are trying to figure out where their sites of disease are and what the burden of disease is by the patient's symptoms. Clearly, this patient has a lot of symptoms of their cancer — they have the weight loss, the fevers and that makes me concerned for advanced disease that I wouldn't be able to cure. In a patient similar to that with a similar radiographic finding but who didn't have those symptoms of illness, I would really want to cross my T's and dot my I's to make sure that we are dealing with, say for instance, the PET scan

shows contralateral lymphadenopathy that's FDG-avid. I feel the need oftentimes to see if we can do a fine needle biopsy of one of the lymph nodes just to make sure that we're dealing with cancer there and that this isn't a node that's reacting to some other thing; some infection or inflammation which can sometimes be false positives on these PET scans. That would be my first thought.

With regard to patients who do in fact have disease involving the opposite side, the contralateral N3 nodes, I think it is a difficult situation, but for the most part I will avoid doing concurrent chemotherapy and radiation, but I would certainly consider radiation after initial response to chemotherapy.

Dr. West: Fair point. Moving on, in this case it is less of an issue because a radiation oncologist who is known and respected in the region has said "Look, this is not a feasible idea." Now she did not have a confirmatory biopsy, but presuming that everything that looked like disease is so.

If you are pursuing with systemic therapy at this point, Greg why don't I start with you in terms of how you would approach the case for somebody who has a very poorly differentiated non-small cell not otherwise specified and a smoking history. You're at Memorial where your program has been ahead of the curve in terms of adoption of molecular markers and I believe that you are routinely screening at least patients with adenocarcinomas. Is the probability of an EGFR mutation low enough in this situation that you would not really be moving down that pathway; or do you rule out just about everybody for any EGFR mutation?

Dr. Riely: We do base our approach largely on histology, so whether a patient has an adenocarcinoma, squamous cell carcinoma or poorly differentiated non-small cell really is an initial break point for us helping us to decide from our molecular analysis pathway. As you said, adenocarcinomas are certainly the patients who are more likely to have the known mutations like EGFR mutations, K-RAS mutation, EML4-ALK translocations; these things that we have heard about so much over the past two years.

The patients with poorly differentiated non-small cell lung cancer are a little bit more difficult to put into bins, if you will. I think that the poorly differentiated is a particularly difficult one and for me always prompts a conversation with the pathologist to find out is this poorly differentiated because we don't have enough tissue, or is it just one of these very undifferentiated tumors. If it's the latter, if it is truly a poorly differentiated tumor, then I think the likelihood of an EGFR mutation is so low that I don't really push for that.

Dr. West: Julie, what's your practice at Hopkins, who as an individual for who you would routinely screen for an EGFR mutation in the first-line setting?

Dr. Brahmer: Actually in this patient, the fact that she only has bronchoscopy-based biopsy, I would have someone biopsy one of these lymph nodes in the supraclavicular region, which should be easy to reach and extremely safe and be able to get much more tissue. We know that one area of the tumor may be somewhat different than another area of the tumor; so you may get more information from a larger biopsy.

Then for EGFR testing, we actually, on any patient that isn't a squamous cell carcinoma, we do send EGFR mutation and that's mainly because of ease. Our pathology automatically sends those out. We also have clinical trials dealing with patients who have K-RAS mutations and so we routinely send those as well.

Dr. West: I think you raise an interesting point that in some places, in many settings, it's much harder to get this information than at the centers where both of you are, which have labs where you can get this done more readily than your average community setting, certainly.

Dr. Brahmer: Right. It's not something that is always done in real time. You have to have a pathologist to tell you do you have enough tissue, and then if you have to send it off; getting the tissue ready to send out does take some time, and also the test itself to get it to the testing site does take some time.

Dr. Riely: I have to emphasize that really the key element in these processes is the pathology department. If as at Julie's institution and our institution where the pathology departments routinely send specimens out, then that cuts out a lot of time in the process, because if a result comes to the medical oncologist and then the decision is made to send the specimen out, that usually adds at least a week into a process that can already take two weeks just from start to finish.

Dr. West: Yeah, and that's been something that we've had, prostate tissue sent for lung work. We've had the wrong, when they need unstained slides, and they'll send stained slides, and then the delays of have multiple centers involved — it can be a real challenge.

Dr. Brahmer: Patience is the key. Patients who want that information, we just have to be patient and be able to sit back and wait as long as people are doing well.

Dr. West: It really depends on the yield, because if it's a high probability you might be more willing than if it's really not that likely.

Let's turn to what systemic therapy, presuming that you even confirm that this is EGFR wild-type and this is somebody who has poorly differentiated non-small cell and a bulky cancer with a fair amount of central disease, but no clear absolute contraindication to Avastin (bevacizumab). Julie what approach would you be inclined to pursue in terms of chemo plus/minus any other targeted therapy?

Dr. Brahmer: In this patient as long as she has no other contraindications to Avastin, I would certainly feel comfortable giving Avastin, and I think with poorly differentiated non-small cell you could give almost any platinum combination, and Taxol/carboplatin and Avastin would be an appropriate combination. The only, I guess, kicker is if at any point you think the radiation oncologist might come back and decide oh, well, we can radiate the existing disease now, Avastin may not be a great idea since there's been some data when Avastin has been combined with radiation therapy or even given after radiation therapy, there can be some local complications. That would be my only concern.

Dr. West: What about as a general question, not this could apply to this patient or anybody, for a poorly differentiated non-small cell where you can't specify histology, is that

somebody who you would be inclined to pursue Alimta (pemetrexed) in the first-line setting; or would you relegate that to later or not at all? That's an agent where if it is more squamous it might not be active.

Dr. Brahmer: Right, I get more nervous giving Alimta to the poorly differentiated, just in the fact that I'm not so sure its going to be that active if acts more like a squamous cell carcinoma. I would probably tend to try that later if the first-line combination chemotherapy did not work.

Dr. West: Greg, what are your thoughts about that?

Dr. Riely: I tend to agree with that. I think probably most of us feel like some of our most broad spectrum anticancer drugs that we use in the first-line in addition to the platinum analogs are the taxanes, and as such I think patients who have poorly differentiated tumors, I lean towards using taxanes as my leading choice. That's not based on any randomized clinical trial, but that's my sense of it.

Dr. Brahmer: Certainly gemcitabine and platinum would also be appropriate as well, and then you could add bevacizumab as well.

Dr. West: So she actually received six cycles of cisplatin and gemcitabine by her local oncologist and she did well with it. She had some fatigue as expected, some low blood counts and dose adjustments. She had a good partial response by a PET/CT at the tail end of that treatment. Her lymphadenopathy in her right neck and the thoracic inlet were not detectable at that point. Much of her paratracheal and left hilar adenopathy also resolved. Her right hilum as well as the subcarinal region still had some residual PET uptake and bulk to it, and the primary mass itself in the left upper lobe had shrunk and still had a significant area of hypermetabolism that hadn't dropped much, but the area within it was much less. That's shown in these images. It certainly does appear to be residual PET-avid disease that probably doesn't represent anything close to a complete response.

But the question is what next? You could approach this as possibly considering radiation at this point or as a good response along the lines of advanced non-small cell and we are starting to now incorporate consideration of maintenance therapy.

So, she had received cisplatin and gemcitabine. She is feeling well, but like many people would be perfectly welcoming of the possibility of a break even if she's a little anxious about being off of it. Greg, what would you be thinking in this situation?

Dr. Riely: Well, I think we've approached this case from the beginning with the notion that this is, although it meets criteria for relatively advanced disease, it's still very localized. As such I would take this opportunity to explore the radiation option and have the radiation oncologist evaluate the patient, understanding that this is not a patient who's really representative in most of the clinical trials in which patients have received chemotherapy and radiation; but also acknowledging that it does hold the chance that this patient can be free of treatment for a longer period of time if they have a good response to radiation.

Now if the radiation oncologist feels it would be too big or that for one reason or another doesn't feel it would be appropriate to give the patient radiation at the time,

when I've given patients gemcitabine/cisplatin as my initial chemotherapy, generally I will continue with the initial treatment of gemcitabine and cisplatin as long as they can continue administer without marked side effects. Often that means dropping the cisplatin but continue on gemcitabine. This flies in the face of a fair number of studies that say that we should discontinue chemotherapy after 4-6 cycles because there doesn't seem to be significant survival advantages to continuing chemotherapy. My perspective on those studies is that they're somewhat underpowered for those analyses, and as such I feel it's appropriate as long as the patient is tolerating the chemotherapy and we seem to be still doing okay with that.

Dr. West: That's interesting. I feel the same way that the studies: many of them have shown the same kind of trends we've seen in the larger studies that have garnered more attention. I think one of the issues has been there's a relatively short list of agents that you can continue feasibly for a long period of time without cumulative toxicity problems. Gemcitabine is one of those.

So you would be inclined towards some form of maintenance therapy and potentially continuing something from first-line rather than stopping and watching for a period of time until things get worse?

Dr. Riely: Exactly.

Dr. West: Julie, what are your thoughts?

Dr. Brahmer: I actually would stop and watch, but watch closely. The more chemotherapy that you give, potentially the less options you may have depending on how well the person's bone marrow recovers after each dose.

I tend to stop and watch at this point, but as I said watch closely, seeing them in person on a monthly basis to talk about symptoms. Then sometimes we'll scan every two months depending on how the patient is feeling and then may spread it out depending on how they're doing. Usually I stop and watch at least in this patient. This maybe different if the histology was , where maintenance pemetrexed, I could use that comfortably in someone with adenocarcinoma. But in someone with poorly differentiated carcinoma, I'd tend to stop and watch.

Certainly radiation therapy would be an option if we really felt that it was safe to give in a local and felt that we definitely give this person a much longer time off of chemotherapy.

Dr. West I'd like to thank both of you for participating. These are tough cases that don't have any clear answers. But covering the thought process really is extremely helpful. I know that it's really gratifying and very helpful for the cancer patient and caregiver population to be able to learn about this stuff. Thank you.

Dr. Brahmer,  
Dr. Riley: Thank you, Jack.