



Current Concepts & Controversies in Locally Advanced NSCLC, Part 1: Multidisciplinary Management of Stage IIIA N2 Disease, with Drs. George Blumenschein and Wally Curran

Dr. West: Hello -- my name is Jack West, I'm a Medical Oncologist in Seattle, Washington and the President and CEO of GRACE, The Global Resource for Advancing Cancer Education.

I'm here today with a couple of very excellent guests, true experts in the field of lung cancer management and in particular within that spectrum of managing locally advanced non small cell lung cancer. That's a multi disciplinary field, so it's fitting to have a couple of experts in two different disciplines. One is Dr. George Blumenschein, Medical Oncologist and Associate Professor in Thoracic and Head and Neck Oncology at the MD Anderson Cancer Center in Houston, TX. Thanks for joining us, George.

Dr. Blumenschein: My pleasure, Jack. Thanks for having me.

Dr. West: And also we have Dr. Wally Curran, who is a Radiation Oncologist and Executive Director at Winship Cancer Center at Emory University in Atlanta, GA. Thanks, Wally, for joining us.

Dr. Curran: Thank you Jack.

Dr. West: Our program this evening is made possible through support from an educational grant from OSI Pharmaceuticals, and they had no input in the development of the content.

Both of the guest faculty had offered their conflicts of interest and didn't have any relevant conflicts of interest to disclose this evening.

So let's turn to a case of somebody who came to see me with a clinical stage IIIA N2 non small cell lung cancer. This is a very fit 54-year-old man who works at Boeing as an aerospace mechanic, and he had been diagnosed with stage IIIA N2 disease, with a cough and some increasing shortness of breath. He had previously smoked a pack per day for ten years, but he had quit decades ago, had this increasing cough and mentioned that to his primary physician. And that led to a chest x-ray that showed a right upper lobe mass that was confirmed on a chest CT just a day or two later. And that CT also demonstrated modest right hilar and what seemed to be potentially some modest mediastinal adenopathy at the 4R region.

He was referred to a pulmonologist at our institution for a bronchoscopy and endobronchial ultrasound. And that revealed that the 4R node had

adenocarcinoma that was TTF-1 positive, so consistent with the stage IIIA N2 disease.

He then, before seeing me, had a PET/CT that confirmed hypermetabolism consistent with cancer involvement in that right upper lobe mass, measuring a little over 4 centimeters -- maximum SUV of 12.6; and also uptake in the right hilum, just really in that 4R node that was not really enlarged just around one centimeter, with some uptake SUV that was consistent with what was seen on the pathology.

So he also had pulmonary function tests before seeing me, and those showed that his pulmonary function tests were certainly compatible with treating him aggressively. And that was his general intent.

So I'll start out with the question of we have staging that confirms at least stage IIIA N2 disease, and we have clinical staging that does not suggest it's more extensive than that. At your institutions, which have very strong multi-disciplinary programs and you probably discuss many of these cases in a multidisciplinary tumor board, would you pursue a mediastinoscopy up front to complete staging, or would you consider perhaps saving the mediastinoscopy until after any pre operative therapy had been done to have the best chance of doing that successfully, given that it can be challenging to do a repeat mediastinoscopy in treated field? George, perhaps you can start.

Dr, Blumenschein: My inclination would be to go ahead and get a mediastinoscopy now to really get a good sense of what the lay of the land is with regards to patient staging. Single site of N2 disease is different than multiple sites of N2 disease, and it would really influence the choice in terms of therapy. I think it's important just to know what the patients are dealing with, in terms of staging up front.

Dr. West: How about you, Wally? Do you feel the same way? And maybe I could just ask with the implication being if there was microscopic involvement of another nodal station, would that profoundly change your management approach?

Dr. Curran: Yeah, Jack, I think it could. This patient might be eligible, and I use the word *might* deliberately, for an approach that involves surgery. There's a lack of randomized data saying surgery would be beneficial, but I think it's a consideration if there's a single nodal site involved. Once you get into multiple nodal sites, whether they're N2 or N3, ipsilateral or contralateral, I really don't think an operative approach would add a lot of benefit for this man

So what you're really doing, in my view, to complete mediastinal staging pathologically is to at least allow for an opportunity of a surgical approach; because if the rest of the mediastinum is otherwise clean, then you can think about the possibility of surgery. If it's not clean, then I don't think surgery should have a role.

- Dr. West:** So he actually did not start with the mediastinoscopy with the thought that that would be saved for later. What is your threshold for recommending the consideration of surgery versus a non operative approach?
- Wally, you and I were involved in a trial years back that never got completed, that was going to look at preoperative chemo versus chemo and radiation for supposed surgical N2 disease that did require just a single station to be involved, but required non-bulky, as in less than say three centimeter nodes.
Are you much more selective than that in your actual clinical practice about who you'd be inclined to recommend surgery for at Emory?
- Dr. Curran:** I think that our policy here is to consider it for fit patients with single nodal station, non-bulky disease. So it's pretty similar to that trial that we developed together. Once you get past one nodal station, I'm not sure that it's easy to justify surgery for such patients.
- Dr. West:** And George, I've been involved in some debates in years past with Steve Swisher at your institution, a great thoracic surgeon -- really good natured debates about whether surgery should be considered a standard of care for selected IIIA N2 disease or not. And so how do you guys approach things? Are you also using single station and not bulky disease as the real arbiter, or do you consider multi station, but ipsilateral you know, same side, N2 nodes as acceptable for surgery?
- Dr. Blumenschein:** I think as a general gestalt is you want to have single station nodal disease involvement. Otherwise we tend to turn toward concurrent chemo/radiation.
- Dr. West:** And what is, do you have a preferred regimen that most or everybody uses as MD Anderson for such patients?
- Dr. Blumenschein:** For induction or chemo/radiation?
- Dr. West:** No, for pre-operative induction.
- Dr. Blumenschein:** We obviously have a great deal of experience with the combination of taxanes and platinum, I think what people are now utilizing in the non-squamous population is pemetrexed plus cisplatin; and in the squamous cell population they're looking at docetaxel and cisplatin. And for patients who can't take cisplatin, they're giving carboplatin.
- Dr. West:** And that's all concurrent with radiation.
- Dr. Blumenschein:** No, that would be induction if we're looking into doing an induction approach before undergoing a surgical intervention.
- Dr. West:** Do you do chemo and radiation in some or many patients before plan surgery?

Dr. Blumenschein: At our institution, no -- that has not been an adopted approach. We make a decision up front in regards to whether we're going to go for a surgical approach or concurrent chemo/radiation approach. In selected cases where it's not quite clear, we will give induction chemotherapy and then reassess; and then based on findings on that point radiographically, make a decision then going forward.

Dr. West: So you don't really use the approach that was used in the Albain intergroup study of cisplatin/etoposide/radiation, and then potentially surgery after that?

Dr. Blumenschein: Correct -- it's not been something that we've adopted as a standard approach here.

Dr. West: Wally, what do they do at Emory routinely? Do you have most patients do chemo alone or chemo and radiation, or is it really selected based on the health of the patient, extent of disease, etc...

Dr. Curran: So for a very small volume N2 disease, we do chemo alone if it is induction. For lesions that have a little more bulk or superior sulcus tumors or other tumors where there's bulk and there's thought to be perhaps also a bulky T lesion, then we do chemo/radiation. So I think in our group it's about a 50/50 split at this point.

Dr. West: So this gentleman was felt to be a candidate for tri-modality therapy, with at least clinical disease that was single station, and he went on to get cisplatin and etoposide for two cycles concurrent with thoracic radiation to 50.4 Gray. He tolerated it about as well as I've ever seen anybody tolerate chemo and radiation concurrently. It was essentially non toxic: I wish I could say that that was always the way it was for patients, but he kept coming in expecting asking, when am I going to give him the real stuff?

Unfortunately his cancer also seemed to have the same kind of response, and radiographically it did not respond well -- or it had a pretty minor degree of tumor shrinkage in the primary tumor. And also his mediastinal node didn't change in any appreciable way.

This is a patient in whom we know the prognosis is not as favorable. Would you say that this is somebody who shouldn't proceed to surgery? Would you use a mediastinoscopy potentially to assess for a "go" or "no go" if he had mediastinal clearance? Or how would you approach such a case? Wally, if you could start.

Dr. Curran: Sure, so from the phase II SWOG study that Dr. Albain and others did, they took the point of view for an induction regimen of etoposide/cisplatin and radiation that a lack of imaging response was not a contraindication to surgery. And in a pre-PET era, what they really found was that there was actually the same sort of result whether or not it was an objective CT scan-based response. And some of those that did not have particularly great CT based response still did well.

Now we know in the PET era that PET is probably a better predictor of ultimate biology and outcome of the patient if you look at PET response to rate chemo or chemo/radiation. In my view, I would say, if the decision had been made to go with the tri-modality approach, the lack of radiographic response wouldn't keep me from wanting to do that.

Dr. West: George what are your thoughts here?

Dr. Blumenschein: In the Albain trial, as long as the patients didn't have progression after they received their 45 Gray of radiation and chemotherapy, they went ahead and had resection in, I think, arm one of the two arms they had. So in this instance, since there is no evidence of progression and the plan was to go ahead and do surgical resection, I think going ahead and doing the mediastinoscopy, and then if it looks like a feasible option, I would resect.

Dr. West: He did undergo a mediastinoscopy and dissection and a right upper lobectomy with that; there was a careful assessment of whether a pneumonectomy would have been required. There was a significant amount of residual viable tumor in the primary mass and also in nodes in the 2R and 4R stations. Others were sampled and were negative.

So he still had residual nodal involvement in two nodal stations, and that's obviously very disappointing. I would say that we had predicted that there was a strong probability at least of nodal positivity in that 4R region; but that really the concern was that you knew that he wasn't going to have a good outcome with chemo and radiation, and so even a relatively challenging course with surgery might be better than the alternative, knowing how disappointingly we were seemingly doing with chemo and radiation.

In these kind of situations, or even just a straight up patient in the Intergroup trial were to get cisplatin/etoposide and RT, if somebody does not have any residual mediastinal involvement are you, George, going to be inclined to recommend post-operative chemotherapy? In other words, would you maybe say, "Well this person did well so they don't need more", or are you going to say, "This person did well with chemo, so we should give more"? What would your general thought process be for someone who does or does not have any residual nodes in the mediastinum after induction therapy?

Dr. Blumenschein: So given that the course of action with this patient mimicked the Albain trial, in that study after undergoing resection patients went ahead and got an additional two cycles of chemotherapy. That was done in both arms; the chemo/radiation arm and the chemo/radiation resection arm. So we don't know that giving the extra chemotherapy made a difference, but given that's how the study was designed and that's where the data came from, I would be inclined to give the patient an additional two cycles of chemotherapy.

Dr. West: There are certainly varying levels of enthusiasm for the emerging molecular marker data, and even considering EGFR inhibitor therapy, testing for an EGFR mutation. Are you personally, or folks at MD Anderson, doing much testing for molecular markers like EGFR or ERCC1 and other molecular markers, to consider giving an EGFR inhibitor outside of a protocol setting in earlier stage disease, or selecting one chemo agent over another because of a molecular marker?

Dr. Blumenschein: We haven't gotten to the point yet that we're using molecular marker to differentiate regards to chemotherapy agents. We have obviously utilized the histology, whether a patient has squamous cell histology or non-squamous cell histology. But we haven't started using the other molecular markers in regards to chemotherapy selection.

In terms of EGFR and KRAS mutational status, that's gaining traction. Not everybody has it done at this point. There are some delays in terms of getting tissue analyzed and results back, so it's not a seamless approach. I think that's where we're going though. It's where we'd like to go at least to kind of establish what a patient's biomarkers are at baseline. It'll help define therapy going forward.

At least in terms of adjuvant treatment after chemo radiation based on the SWOG study, the S0023, I would not give this patient a targeted agent afterwards, specifically gefitinib or erlotinib.

Dr. West: Wally, in a patient who has residual mediastinal disease, if they turn to you at the tumor board and say, "Is there any rule for any more radiation?", what would you say in terms of both feasibility and advisability?

Dr. Curran: In this particular patient, I would not recommend it. I think the ability to give a significantly additional meaningful dose really isn't there.

Now the other scenario that sometimes occurs is a patient will have received pre-operative chemo/radiation and then resection is incomplete for a variety of reasons: is it then feasible to go back after recovery from thoracotomy and add dose? We sometimes do it, but I don't know how much it benefits a patient. But clearly for this type of setting, I would not recommend additional radiation.

Now this type of scenario has led certain groups, including the RTOG, with preliminary data from the University of Alabama, Birmingham, and University of Maryland to execute a trial where a more full dose of radiation is given with concurrent chemo prior to resection - a dose up to 60 Gray, with the idea that you've given all the radiation you're ever going to give, probably, you might have a higher likelihood of nodal clearance with the higher dose of radiation.

And what we know so far, based on the RTOG trial is that this was feasible -- the complication rate was not any higher, and we're just at the point where perhaps at ASTRO this year we'll be able to look at the

complete tumor clearance rate in a multicenter perspective trial with 60 Gray and chemotherapy concurrent.

Dr. West: How large a study was that in terms of number of people and also the centers participating? Because I would say our center was also influenced by learning more about the University of Alabama experience by Dr. Cerfolio and some other places that are doing this work.

Wally: I think the total number of patients was between 60 and 70, and there were over a dozen centers participating, so it was beyond the two academic centers which had done a lot of institutional work before then.