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Traditional Approaches to Treating NSCLC, Part 2: Neoadjuvant Combined Modality, Locally Advanced, and Metastatic NSCLC

Transcript - Traditional Approaches for Treating Non-small Cell Lung Cancer

for Neoadjuvant Combined Modality Therapy of Locally Advanced as well as

Management of Metastatic Non-Small Cell Lung Cancer with Dr. Shirish Gadgeel

Narrator Opening:

Welcome to Project Oncology on ReachMD. This is the Prova Education activity: Immunotherapy in Non-Small Cell Lung Cancer. This is part 2 of our conversation on traditional approaches to treating NSCLC for Neoadjuvant Combined Modality, Locally Advanced, and Metastatic NSCLC.

Your host is Dr. Mohammad Jahanzeb. Dr. Jahanzeb will speak with Shirish M. Gadgeel, MD who is a Professor of Medicine and Oncology and a Leader of the Multidisciplinary Thoracic Oncology Team at the Karmanos Cancer Institute in Detroit, MI.

Dr. Gadgeel MD is a consultant for Boehringer Ingelheim, Genentech, Novartis, Pfizer.

Dr. Jahanzeb is a consultant for Roche, Genentech and Novartis and has disclosed contracted research with Genentech, AbbVie and Lilly.

This CME activity is supported by an independent educational grant from Merck.

After listening to this educational activity, participants should be better able to:

1. Evaluate the clinical utility of traditional approaches to treating potentially-resectable Stage III and metastatic NSCLC

2. Discuss the potential impact of targeted drug agents and use of biomarkers on outcomes for NSCLC

Dr. Jahanzeb:

On today's discuss we'll discuss Immunotherapy Non-Small Cell Lung Cancer. This is part 2 of our conversation on Traditional Approaches for Treating Non-Small Cell Lung Cancer for Neoadjuvant Combined Modality Therapy of Locally Advanced as well as Management of Metastatic Non-Small Cell Lung Cancer.

I'm your host, Dr. Mohammed Jahanzeb, and joining me today is Dr. Shirish Gadgeel from Karmanos Cancer Center in Detroit, Michigan. Dr. Gadgeel, welcome to the program.

Dr. Gadgeel:

Thank you very much, Dr. Jahanzeb.

Dr. Jahanzeb:

My pleasure. In Part 1, as you know, we discussed treatment approaches for Stage III unresectable non-small cell lung cancer and you did actually cover aspects of combined modality therapy, but we did not specifically get into the nuances of neoadjuvant therapy vis-à-vis combined modality intervention in general. So, can you elaborate on that and tell us where you would use neoadjuvant therapy?

Dr. Gadgeel:

So, what I would say is if you look at resectable Stage III disease, I sort of categorized that into 2 groups. One is, there are patients who, despite all appropriate preoperative staging, are found to have microscopic mediastinal lymph node involvement at the time to surgery, so these are patients who are not known to be Stage III disease undergo surgical resection and are found to have positive mediastinal lymph nodes. So these patients after surgery would be considered for adjuvant chemotherapy. And based on retrospective data, both of randomized trials as well as theories from SEER, S-E-E-R, we do consider after adjuvant chemotherapy mediastinal radiation.

However, I think the more common scenario are patients who are known to have Stage III disease but what one could consider potentially limited Stage III disease, and I would say what I mean by that is, probably 1 or 2 lymph node station involvement and also non-bulky involvement. And as I mentioned earlier, bulky lymph nodes would be considered as 3 cm or greater. In general, in this situation we would consider T3 tumors; although, clearly T4 tumors can be surgically resectable, but usually the scenario would be a T3 tumor with 1 or 2 lymph node stations.

Now, there are randomized studies that have looked at such patients of using both concurrent chemotherapy radiation followed by surgery versus just doing concurrent chemotherapy and radiation. What the studies have shown is that there is no evidence that this approach of trimodality approach necessarily improves survival compared to concurrent chemotherapy alone. However, in retrospective analysis what was noted is that in patients who didn't require a pneumonectomy, there was evidence of a survival advantage, so patients who required a lobectomy did appear to have a survival advantage. Now, this was a retrospective analysis, and therefore, in this situation pretreatment assessment of what sort of surgery would be required is very essential, and if it is felt that a patient won't need pneumonectomy, then approach of concurrent chemotherapy and radiation followed by surgery, or for that matter chemotherapy followed by surgery, would be considered appropriate.

It is not clear that you need concurrent chemotherapy and radiation as opposed to chemotherapy alone. Randomized studies have

been attempted to address this issue but have failed to accrue enough number of patients. At our institution the approach is to do concurrent chemotherapy and radiation and then take the patient to surgery, but there are definitely institutions that just consider chemotherapy.

The two other points I would like to make is this is one clinical scenario where it is extremely important that a multidisciplinary approach right from the beginning is embarked upon, and this is one area where I would strongly urge that we consider particularly surgeons with expertise of resecting tumors following chemoradiation, chemotherapy and radiation, because these patients potentially could have high rates of morbidity and mortality, and therefore, this is one area where referring patients to surgeons that have adequate experience would be quite important.

The last thing I would say is that the consensus is to be very selective in the patients where we consider this approach, and that is what I meant by choosing patients who have possibly limited N2 involvement. And as I mentioned, we consider limited involvement as either 1 or 2 stations or non-bulky lymph nodes.

Dr. Jahanzeb:

So, Dr. Gadgeel, how do you define Stage IV metastatic non-small cell lung cancer? And let's talk about therapeutic options for these patients based on myriad sites of disease spread if you think that's relevant.

Dr. Gadgeel:

Right, so one important thing when we consider for Stage IV disease is that in the recent staging system, Stage IV disease now has 2 subcategories, IVA and IVB, so the reason it is subcategorized is the prognosis of Stage IVA patients is better than, somewhat better than, Stage IVB patients, and Stage IVA patients are patients who's metastasis is either limited to the lung or has extended to the pleura, and any metastases to other areas outside of the lung and pleura is considered IVB. The standard treatment for these patients is systemic therapy, and this is where the assessment of molecular markers and histology has become very relevant in discussing systemic therapy. And we will discuss this in greater detail in the subsequent questions, but as far as major sites are concerned, I think one area of management that is becoming a focus of attention is management of brain metastases where, because we now routinely do brain scans in Stage IV patients, we tend to detect patients who have limited number of brain metastases, and in many of these patients we consider very focused radiation, stereotactic radiotherapy, instead of whole brain radiation. And then we can continue to implement the stereotactic radiotherapy as in when further brain metastases show up, and the use of whole brain radiation has clearly declined.

The other aspect as far as sites of metastases is concerned is that in patients who have specific areas of metastases, and particularly in a situation where there are isolated areas of metastases—what I mean is isolated brain metastases or isolated adrenal metastases—a surgical approach can be considered. This is a very select group of patients who have what we would consider early-stage disease outside of the metastatic area, generally patients who don't have mediastinal lymph node involvement and where the patient is in a position to undergo surgical resections.

My usual approach in these patients who have what we would consider as isolated solitary metastasis is to treat the patient initially with appropriate systemic therapy just to ensure that these patients don't develop any other areas of metastases. And then if they have had a good response to treatment or at least stable disease with no other areas of metastases and no progression of disease, then local therapy both to the primary as well as to the metastatic area can be considered. And in theories, not in prospective data but in theories, this has shown to provide improved survival.

The local therapy to the primary or to the metastases can either be surgery or radiation based on the location and based on the feasibility of EDsmortalities. Treatment of solitary metastases we do consider local treatment following systemic therapy. This is now being extended to oligometastatic disease as well, particularly in patients who have molecular marker positive tumors. So if patients have EGFR mutation positive tumors or ALK rearrangement positive tumors, after treatment with appropriate targeted treatment, if local

treatment to oligometastatic sites can be considered, though again we don't have prospective data to show that it prolongs survival. The theories data, single arm theories data has suggested that the cancer remains, that there is improved disease control for a longer period of time in these patients.

Finally, in patients who are treated with targeted treatments, occasionally some of these patients have focused area of, or solitary area of progression, and in these patients local treatment of that particular area, again either with surgery or radiation, can be considered with the hard process that this is one area where the cancer has become resistant to the targeted treatment; but in other areas of metastases, the cancer remains sensitive, and therefore, approaching the isolated area of progression with local treatment followed by continuation of the targeted treatment will allow us to control the disease for a longer period of time. And there are data sets in EGFR and ALK mutation positive patients that show that further control ranging at a median of 4 to 7 months can be achieved with such a strategy. So, the general approach for management of Stage IV disease is assessment of histology, assessment of molecular markers, and then based on the sites of disease deciding whether any local therapy can be integrated with systemic treatment.

As far as histology, as far as patients who don't have molecular alterations that can be targeted, the primary treatment remains platinum-based chemotherapy, and the choice of platinum-based chemotherapy is based on histology. In squamous cell patients we choose a platinum-based combination that does not include pemetrexed because of lack of efficacy of this drug in these patients, in patients with histologic tumors; whereas, in nonsquamous patients we can consider pemetrexed and a platinum-based combination. In select nonsquamous patients, bevacizumab can be integrated with the platinum-based combination based on ECOG 4599 that showed improvement in survival, but this is being done on a very selective basis. The standard of care now is to do about 4 to 6 cycles of the 2-drug combinations and then subsequently, at least in non-squamous patients, follow it up with pemetrexed maintenance. Erlotinib has also been approved as maintenance therapy, but the use of erlotinib as a maintenance therapy in patients whose tumors are not EGFR mutation positive is quite limited despite its approval.

And then the other important aspect of management of Stage IV is to obtain molecular markers, specifically EGFR, ALK and increasingly now also RAS1. And the reason for obtaining these molecular markers in the front-line setting is because we have clinical data to show that use of targeted agents in patients with tumors that have these molecular alterations provides better and a longer tumor control than platinum-based chemotherapy. So in EGFR mutation positive patients we have the choice of either using erlotinib or afatinib. In patients with ALK rearranged tumors, we use crizotinib. And though there is no randomized data for RAS1 alteration positive patients, patients with RAS1 alteration positive tumors, there is Phase II data to show that crizotinib provides quite… demonstrates very good progression-free survival with a median of 19 months in these patients. There are other molecular markers which at the present time are not a consideration at least in the front-line setting.

So in summary, the knowledge of histology, knowledge of molecular alterations and the sites of disease has become very important in deciding appropriate therapy for a particular patient.

Dr. Jahanzeb:

Wonderful. That was an excellent summary. Now let's talk a little bit about recurrent disease. These are patients who have been treated definitively for cure but unfortunately recur. How does one select the next intervention?

Dr. Gadgeel:

So in general, patients with early-stage disease who do recur are generally approached the same way as we approach Stage IV lung cancer patients. I think the 2 considerations… the 1 primary consideration that I give in deciding therapy is the duration from the last systemic therapy. So if the patient has recurred within 6 months off using a platinum-based 2-drug combination, then in those patients I'm more than likely to use a second-line chemotherapy, usually single agent, as I would do in a Stage IV patient who has relapsed. However, if the patient has relapsed more than 6 months and is in good performance status, I may consider using a platinum-based 2-drug combination again in such patients. Again, in these patients of recurrent disease, molecular testing is very relevant either using prior resected specimen or prior biopsy or a new biopsy to determine EGFR and ALK rearrangements. And if any of these molecular

alterations are detected, then appropriate targeted therapy is what I would use.

So at the present time, what I would state is the patients who have recurrent disease, the treatment options would be similar to Stage IV lung cancer patients. However, the only difference would be that if the patients have recurred relatively soon after the use of prior systemic therapy, then in those patients, more than likely, I would use single-agent therapy, which are commonly used in second-line treatments such as docetaxel.

Dr. Jahanzeb:

If you're just tuning in, you're listening to Project Oncology on ReachMD, the Channel for Medical Professionals. I'm your host, Dr. Mohammed Jahanzeb, and today I'm speaking with Dr. Shirish Gadgeel for Part 2 of our conversation on Traditional Approaches to Treating Non-Small Cell Lung Cancer for Neoadjuvant Combined Modality, Locally Advanced as well as Metastatic Non-Small Cell Lung Cancer.

In terms of, let me just talk a little bit about local recurrence, so you of course were talking about systemic recurrence; if a patient has a mediastinal lymph node that turns out to be PET-positive and biopsy-positive after definitive treatment, you would treat them as de novo inoperable Stage III or would you do something different?

Dr. Gadgeel:

So, yes, you're absolutely right that the patient, of course, can have local regional recurrence. So if they have mediastinal lymph node recurrence, that in most of these patients I would consider chemotherapy and radiation assuming that that's the only site of recurrence. Occasionally, you can have recurrences at the site of resection without any evidence of recurrence within lymph nodes. This is not very common, and in those patients a consideration could be made for the surgical resection; though this is a very unusual situation.

You occasionally do see regional recurrence following concurrent chemotherapy and radiation without any evidence of systemic recurrence. In these patients many times doing further radiation can be challenging because of recurrence within the field of radiation therapy or significant overlap with prior radiation fields, and in these patients the only option is systemic therapy. So clearly when patients have local or regional recurrence, local therapy can be considered in appropriate settings, but in most cases use of systemic therapy is required.

The last thing I would mention is that it is very important to be cognizant of the fact that these patients who have lung cancer can develop a second primary, and this can happen even a few years after the original primary, the first primary, has been treated. And so every new lesion detected on a CAT scan, on a follow-up CAT scan, should not be considered as metastases, and appropriate consideration should be given that particularly an isolated lesion could be a second primary. In that event it should be approached as one would approach a newly diagnosed early-stage lung cancer.

Dr. Jahanzeb:

That's a very important point. Let me jump a little bit to emerging information from clinical trials. What new and exciting data are being reported? Please also shed some light on the potential value of targeted agents in the treatment of non-small cell lung cancer.

Dr. Gadgeel:

I think the most exciting advances are, outside of immunotherapy, are therapies based on molecular alterations in non-small cell lung cancer. So we've already discussed EGFR and ALK, and based on recent data by the Lung Cancer Mutation Consortium published in *JAMA*, it appears that at least in adenocarcinoma patients in about 60 to 70% of the patients a driver genetic alteration can be identified, and one speculates that appropriate use of targeted therapy in these patients will also provide additional benefit, will provide similar

benefit as observed in patients with EGFR mutations and ALK translocation.

The other emerging data is that with these targeted agents, as you very well know, the tumor eventually does develop resistance, and we are learning more and more regarding the resistance mechanisms. And so, we have now new drugs that are based on an understanding of the resistance mechanisms to the first generation drugs, and these drugs that are being assessed in patients who develop resistance have shown very promising results. And in fact, several of these drugs have received breakthrough designation with the expectation that they will be available to treat patients who have progressed on first generation drugs. So we have now patients, and yes, that percentage is still very small, who have Stage IV lung cancer and we have not treated them with chemotherapy despite these patients having Stage IV lung cancer for sometimes 2, 4, 5 years. And I generally believe that that's an advance because these drugs in general are better tolerated than systemic chemotherapy, primarily because they target a molecular alteration that is much more relevant in the cancer than in normal tissues. And so, I think those 2 are the primary advances that I would highlight.

The only other thing I would say, and though we are going to have a more thorough discussion of immune therapy, there is emerging data that immune therapy potentially could be combined with targeted therapy, and this may provide even greater benefit than what we are observing with our targeted agents. So in EGFR mutation positive tumors, there are now trials and some limited data of combining anti-PD1 drugs with EGFR tyrosine kinase inhibitors. Similar efforts are about to be launched or have already started in ALK translocation positive tumor patients. So, we may be able to integrate these treatments to provide even better tumor control than what we are doing right now, so it's clearly a very exciting time for clinical research in non-small cell lung cancer.

Dr. Jahanzeb:

Great, I agree this bodes very well for our patients. And we have been talking about responses and progression-free survival, survival improvement. We haven't quite touched on quality of life. What is the quality of that additional time that patients can? Do you want to touch on that briefly?

Dr. Gadgeel:

Yes. I think that because of these drugs being more effective, I think the biggest impact on the quality of life is since the tumor is better controlled… As you very well know, in lung cancer patients the major impact on quality of life is because of symptoms and effects of lung cancer, and since these targeted drugs control the cancer much better than systemic chemotherapy, the improvement in symptoms and therefore the quality of life is much better than what we see with chemotherapy. Of course these drugs do cause adverse effects, but these adverse effects are far more manageable. So I think we have not just improved overall survival. I do believe because of better tumor control we have also improved quality of life.

Dr. Jahanzeb:

Great. Any final thoughts for our colleagues?

Dr. Gadgeel:

The only thing I would say is that I think it is incumbent upon treating physicians that we truly try and assess our patients thoroughly, and this doesn't mean just clinically but also pathologically and molecularly, molecular assessment of their tumor, because I think that that is going to provide us with our best chance of treating our patients with the most effective treatment. And I think that now with all the different drugs that are available, it is even more important that we make an effort to enroll our patients on clinical trials because I do believe that we have more effective drugs in clinical trials right now than what we had in the past, and enrolling in a clinical trial may provide, potentially provide, the best option for the patient in terms of disease control and improving survival.

Dr. Jahanzeb:

I couldn't agree more. That's excellent. That's why every period of NCCN guidelines says at the bottom, “The best option for a cancer patient is enrollment in a clinical trial.”

So with that I very much want to thank our faculty, Dr. Gadgeel, for enlightening us about more advanced lung cancer and various biological approaches, targeted approaches, and the emphasis on enrollment in clinical trials, or at the very least, assessing our patients for biomarkers and individualizing therapy, customizing their treatment. Dr. Gadgeel, thank you so much for your insights.

Dr. Gadgeel:

Thank you very much.

Narrator Closing:

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