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Neoadjuvant and Adjuvant Therapy in Early-Stage NSCLC

Announcer:
You're listening to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. Your host today is Dr. Steve Jackson.

Dr. Jackson:
This is *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Steve Jackson, and today, I'm joined by Dr. David Carbone to talk about neoadjuvant and adjuvant therapy for non-small cell lung cancer. Dr. Carbone is the Barbara J. Bonner Chair in lung cancer research at the Ohio State University Comprehensive Cancer Center in Columbus. He also serves as the Director of the James Thoracic Oncology Center and co-leader of the Translational Therapeutics Program. Dr. Carbone, welcome to our program.

Dr. Carbone:
Dr. Jackson, it's great to be here.

Dr. Jackson:
With more neoadjuvant, perioperative, and adjuvant options now available for non-small cell lung cancer, how have those newer options changed the way you approach a newly diagnosed patient?

Dr. Carbone:
Well, neoadjuvant therapy has been transformational in the management of early-stage lung cancer. Historically, we would assess and stage the cancer, and if there were positive nodes in the mediastinum, we would do chemoradiation, and if not, we would go straight to surgery and give adjuvant chemotherapy. And in those days, half of patients would recur and die, even with complete resections, and the adjuvant chemotherapy added only perhaps five percent improvement in long-term survival.

But now, multiple studies have shown that neoadjuvant chemoimmunotherapy dramatically improves the outcomes, and in fact, does so even with multistation N2 disease in the mediastinum, where, even with that involvement, we sometimes see pathologic complete responses. And so I think it's a new paradigm in the treatment of early-stage lung cancer.

Dr. Jackson:
And which biomarkers do you want the results for before making a treatment timing decision? And how do you handle testing on the diagnostic biopsy at the start versus what you might see with the resection specimen?

Dr. Carbone:
So this new approach has resulted in a complete change in the way we view biomarkers for lung cancer. Historically, surgery didn't rely very much on biomarkers. If it was resectable non-small cell, it would get resected. And the adjuvant therapy was pretty much the same for a given histology.

But now we need to know molecular biomarkers before surgery, absolutely, 100 percent of the time. If there's a driver mutation—EGFR, ALK, ROS—then the perioperative management is completely different. And currently, it's been shown that outcomes are improved if you use adjuvant-targeted therapies for EGFR and ALK, and, by presumption, other driver mutations. And that neoadjuvant chemoimmunotherapy has the best outcomes for non-driver mutant tumors, including KRAS, which does muddy the waters a bit, because it's clearly a driver, but it also has improved outcomes with chemoimmunotherapy.

Dr. Jackson:
Once the biomarker results are in hand, what clinical factors push you toward neoadjuvant therapy, a perioperative approach, or just going straight to surgery followed with adjuvant therapy?

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Dr. Carbone:
The decisions have become complex, for sure, but I think today it's very clear that any node-positive lung cancer should receive neoadjuvant chemoimmunotherapy, and that's N1 or N2. And it's now even being tested whether the earliest stage 1A tumors may even benefit from immunotherapy as well.

I think any tumor right now over three or four centimeters in size, or for sure any tumor with N1 or N2 disease, should have neoadjuvant therapy. And the only tumors that I give only adjuvant immunotherapy to are the ones that are found to have more advanced stage at the time of surgery—N1 or N2 nodes that were discovered at the time of surgery and thought to be negative initially.

The other biomarker in this space is PD-L1. And it's very clear that patients with PD-L1 negative tumors don't do as well as high PD-L1 positive tumors. But with the current state-of-the-art, we use chemoimmunotherapy in all PD-L1 states, so PD-L1 really doesn't change our management of these patients. PD-L1 does affect adjuvant immunotherapy in my mind. And that's most strongly seen in the adjuvant atezolizumab study, where really all of the benefit for adjuvant immunotherapy with atezolizumab was in the high PD-L1 subgroup, with, in fact, a trend toward harm in the PD-L1 negative group. So in my practice, I use adjuvant atezolizumab only in the PD-L1 positive patients and not PD-L1 negative, which is the way it's approved in Europe.

The other biomarker that's important in the operative specimen—so after neoadjuvant chemoimmunotherapy—pathologic response. About 20 to 30 percent of these patients achieve a pathologic complete response. Another large fraction has a major pathologic response, and some patients don't have a response at all and still have a high tumor percentage in the resection specimen.

Dr. Jackson:
For those just joining us, this is *On the Frontlines of Non-Small Cell Lung Cancer*on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. David Carbone about neoadjuvant and adjuvant approaches.

Dr. Carbone, for patients who receive neoadjuvant therapy, how, if at all, does pathologic response factor into what you recommend after surgery?

Dr. Carbone:
So that's an excellent and controversial question. It is certainly prognostic. Patients with a complete pathologic response in the tumor, which is not rare, do extremely well, and, in many studies, have a near perfect survival. Patients with lower degrees of pathologic response do less well, though it's completely unclear right now whether those differences in prognosis can be effectively translated into different therapies to improve outcomes.

And I think the feeling in the community is that patients with non-pathologic CRs should have adjuvant therapy, though the data don't really support the use of I-O monotherapy in the adjuvant setting, in my interpretation, as the outcomes with neoadjuvant chemoimmunotherapy alone in CheckMate 816 are as good as other studies that include 77t, which also uses chemo-nivo, and adds a year of adjuvant immunotherapy after surgery.

So I think the general oncology thought is that people who don't have a pathologic complete response should have a year of adjuvant immunotherapy, though there's really no data that show that that benefits anything. I personally believe that if you don't have a pathologic complete response, you do need additional therapy, but that we need to think about changing that therapy, adding to that therapy, or intensifying therapy, and not just giving another year of the same immunotherapy that wasn't effective before surgery.

But it's very clear to me that the neoadjuvant phase is the most important phase. And in my general practice, I use the CheckMate 816 regimen and usually do not use adjuvant immunotherapy. I also look for clinical trials in that setting.

Dr. Jackson:
And what are the key considerations for managing treatment-related adverse events and surgical timing across the multidisciplinary team in these different settings?

Dr. Carbone:
Well, lung cancer, certainly, is a disease best handled by a multidisciplinary team. And in our clinic, my surgeon is on my left, my interventional pulmonologist is on the right, and the palliative care person is behind me. So we work together with these patients, evaluating biomarkers and patient fitness before surgery, and following them through their neoadjuvant phase and postoperative care.

One advantage to the CheckMate 816 regimen is that it's only three cycles of chemo-nivo, as compared to four cycles in most of the other regimens. And I think, again, the outcomes of the three cycles of neoadjuvant only are indistinguishable from four cycles with adjuvant. And I think that that gives a higher probability of not interfering with surgery due to side effects that are observed in the neoadjuvant phase. Patients can get pneumonitis, they can get colitis, they can get hypothyroidism in the neoadjuvant period, and they

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need to be followed very closely. They can get pancytopenic from the chemotherapy. But I think, overall, these patients, when managed with standard techniques, get through the neoadjuvant phase, especially the three cycles, just fine.

And we very rarely interfere with the ability to do surgery. And those few patients where we do find that surgery is not the best option after neoadjuvant likely had aggressive tumors that would not have done well, even if they had gone straight to surgery. So I think that we are definitely benefiting these patients with neoadjuvant chemoimmunotherapy, and we very rarely interfere with surgery.

Dr. Jackson:
And lastly, what other open questions or ongoing research do you see as most important for the future of neoadjuvant and adjuvant care in non-small cell lung cancer?

Dr. Carbone:
Well, we haven't talked much about the targeted therapies, but clearly these principles are being tested with targeted therapies in neoadjuvant and adjuvant settings, so I think that's still an important line of research.

I think it's important to know how long we need to continue adjuvant therapy, whether we can dose-intensify adjuvant therapy, and how we're going to use some of the new therapeutic bispecific antibodies, especially in perioperative therapy, with ivonescimab or other bispecific antibodies.

And I think a big question in the field is also, perhaps, how to best integrate minimal residual disease monitoring with blood biopsies into this decision-making, if some of these patients are cured at the time of surgery and could be spared additional therapy. Could we use minimal residual disease testing to spare those patients additional therapy or dose-intensify, if the disease is not controlled in the blood?

So there are many research questions. Adding KRAS inhibitors in this setting, for example, or antibody-drug conjugates, all are actively being investigated.

Dr. Jackson:
Okay, thank you. Now that was a very well-delineated approach to the treatment timing considerations of NSCLC. A big thanks to my guest, Dr. David Carbone, for joining me to talk about neoadjuvant and adjuvant approaches to non-small cell lung cancer. Dr. Carbone, it was great having you on the program.

Dr. Carbone:
Pleasure to be here, Dr. Jackson.

Announcer:
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