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Pre-Operative Considerations in Neoadjuvant Therapy for NSCLC

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Dr. Forde:
In this episode, we're going to discuss some of the pre-operative considerations when discussing neoadjuvant therapy for non-small cell lung cancer. First of all, I'm going to ask Dr. Tricia Cottrell who is a pathologist to go over some of the considerations we have in terms of testing for patients when considering neoadjuvant therapy.

Dr. Cottrell:
Thank you, Dr. Forde. I think our pathology departments have a really important role in making sure that we are expediting pre-treatment testing results. I think it's important that pathologists expedite pre-treatment testing results so that patients who are confirmed as having mutations for ALK-EGFR receive the appropriate therapies as they would be excluded from the current approval for neoadjuvant treatment.

Dr. Forde:
Yeah, I think that's a key point and something which, for us as medical oncologists, we really have to consider with these therapies. CheckMate 816 and all of the other neoadjuvant trials have excluded patients with EGFR and ALK. To move to Dr. Peters, just to ask her some considerations medical oncologist may have in terms of getting a patient who is newly diagnosed with lung cancer through neoadjuvant therapy to surgery and some of the figures on that.

Dr. Peters:
Yeah, thanks a lot. I think we are experiencing a new era of opportunities. Thinking and considering the administration of neoadjuvant chemo IO even in Stage II disease, right? Meaning that we were pretty used to consider neoadjuvant chemotherapy for Stage III. It was even, we could say, evidence-based, but now the idea is not on the chemo, it is chemo/IO, and it is in early disease, Stage II, Stage III even, Stage 1B - more than four centimeter.

So it is really expanding it with a concern that if we want to really be conservative and looking at data with a kind of scrutiny or a little bit of, I would say all the worries that we could have by changing the paradigm of surgery first, we have been seeing across trials that we have in hands now a certain number of patients who are screened and enrolled in the trial for neoadjuvant chemo versus neoadjuvant chemo/IO who do not reach surgery, who are not resected at the end, it's between 7 and 17% of the patients. You will probably ask me, does it happen in real life? Yes, probably because some patients progress under neoadjuvant chemo or chemo/IO, some patient refuse to go to surgery, some patients have toxicities. But the question is, are these 7 to 17% more than what you would expect in real life? I'm not sure we have the answer, but we have to keep it in mind by implementing a new strategy. You should never take the risk of making the surgery impossible. And I think we need more trials and more data to make sure it is not the case.

Dr. Forde:

Perfect. No, I think that's a key consideration when we're discussing these options with patients. Neoadjuvant therapy is a wide funnel. We're essentially taking everyone who's coming in the door newly diagnosed with lung cancer and offering them, not quite a new approach, but something which has not been used widely up until recently. Just move on to Dr. Spicer, who's a thoracic surgeon, and maybe to get your perspective, Jon, on neoadjuvant novel approaches and neoadjuvant therapy, how a surgeon might approach that and consider it.

Dr. Spicer:
Yeah, and to sort of dovetail with what Dr. Peters was saying, this concern of missing a window to curative surgery is really perhaps one of the most current and frequent refrains we hear. We have to remember that the trial data around neoadjuvant versus adjuvant show pretty much equivalent survival gains when we're talking about conventional chemotherapy. Those comparisons can be criticized because as you said, neoadjuvant is a wide funnel of patients and some might not make it to surgery, whereas adjuvant trials tend to be selected patients who actually get to adjuvant therapy. But a lot of people forget the MATCH data, which is pretty much our only fully accrued trial comparing surgery as an upfront and only modality surgery with adjuvant therapy versus neoadjuvant chemo followed by surgery. And what was very clear from that trial is that there was no harm incurred by the application of neoadjuvant chemotherapy. If anything, the disease-free survival was numerically superior in those patients. So, the argument to say that by giving neoadjuvant treatment you may compromise the patient's long-term outcome is not really born out by high quality trial data. And that was 15 years ago with perhaps more toxic and less effective systemic therapy regimens. So, while I hear the concerns about the 17% rate of non-progression to surgery in CheckMate 816, I was reassured by the NADIM II data where we saw only 7% of patients in Stage IIIA and IIIB not making it to surgery. And then I think the final point I would have about this is centers will have to look at their own performance and their own data and their own ability to get patients through the full treatment trajectory. What is I think unquestioned regardless of the strategy you employ is that a full treatment course is what offers the best treatment plan. And certainly, in our environment, the vast, vast majority of patients who are assigned to neoadjuvant regimen will make it to the operating room.

Dr. Forde:
Yeah, I think those are great points, Jon. The one thing I might bring back a little bit to Dr. Cottrell is, so as an immunopathologist, what are your thoughts on, not so much theoretical benefits in terms of immunotherapy specifically in the neoadjuvant setting, but we do have some data on this, some mouse studies, some data from your own work suggesting that perhaps there are practical scientific benefits to using neoadjuvant immunotherapy as opposed to adjuvant. What are your thoughts on that?

Dr. Cottrell:
Yeah, I think that's a great point and I do wear multiple hats in terms of immunology as well as pathology. I wanted to add, I think from the pathology perspective of getting patients to surgery. It is critical that the genomic testing be performed in an expedited manner. And I know that there's variation across sites where some places do reflex testing of pretreatment biopsies that are adenocarcinoma and others don't and it requires a clinician to initiate that testing. So I think working with pathologists to streamline those workflows is certainly a piece that would help the neoadjuvant therapy gets started sooner and hopefully, increased rates of patients getting to surgery.

In terms of the immunology, I'd like to emphasize that this is a whole new world in terms of therapy. The mechanism of immune checkpoint blockade is very different from chemotherapy. So, with immune checkpoint blockade, we're specifically looking to activate an anti-tumor immune response. And we saw in CheckMate 816 that PD-L1 immunohistochemistry actually does enrich for patients who are more likely to respond. So those patients who had more than 50% PD-L1 expression on their tumors, the highest rates of response. So, I think there are potential roles for actually using pretreatment biomarkers to select the subset of patients that are most likely to respond to neoadjuvant therapy. We also know that in patients who have cold tumors where there's not an immune response present, that response to particularly single agent anti PD-1 is particularly unlikely. So I think having additional data to support actually selecting patients based on the likelihood of response is certainly going to be one way that we're able to increase the rate of patients getting to surgery moving forward.

Dr. Forde:
Yeah. No, I think that's an excellent point. And I guess Dr. Peters, how do you approach a discussion about neoadjuvant versus adjuvant with a patient? So, say you have someone comes into your clinic tomorrow with Stage II lung cancer. How do you approach that discussion?

Dr. Peters:
So it is nice you take the Stage II because for Stage III it is a discussion we already had since as I said before, since some years, right? For Stage III, for me it makes sense for many reasons including the resectability and the ease of the surgery I have to resect afterwards. For Stage III, for me neoadjuvant is obvious, but for this Stage II, I think we still have to really manage to handle a fair discussion with the patients, right?

The patient is usually expecting to start with surgery and you have to explain why as it was said before immunologically it might make sense to revert the sequence. And on the other hand, the idea is that anyway the treatment is delivered at some time point before or after. Of course, the assessment is not exactly the same. Clinical staging is different from a pathological staging, but there is a rationale (immunologically and biologically) to think that the immune response might be better in a clonal naive tumor being in place as compared to, I would say a treatment that should be given in a patient who is completely resected. And I must say, my discussion has changed a bit into more an incentive to maybe accept the neoadjuvant, since we have seen the melanoma data.

You remember melanoma is the disease paving the way to immunotherapy, right? And we had this nice trial presented at ESMO meeting this year, just thinking about giving the whole adjuvant pembro melanoma after surgery or just anticipating three cycles before surgery, and the outcome was so much better by anticipating three cycles before surgery. So maybe we are not melanoma doctors, but something about the immune response gives me some incentive at least to propose it to the patient knowing that compliance might be better in any way for these patients. Surgery and IO are the rules, right?

Dr. Forde:
Perfect. I think those are points we are going to definitely expand on in some of the other episodes in this series. I think we have had a good initial discussion here about those first considerations when we have patients coming in the door, and I think there are several other episodes where we are going to discuss these in more detail. So feel free as learners to join those episodes. Thank you for joining us today.

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