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www.reachmd.com
info@reachmd.com
(866) 423-7849

Perioperative Immunotherapy Strategies in Resectable NSCLC Care

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me today to discuss the structure and rationale of perioperative immunotherapy regimens in resectable non-small cell lung cancer is Dr. Martin Dietrich. He's a medical oncologist with the US Oncology Network Cancer Care Centers of Brevard and an Assistant Professor of Medicine at the University of Central Florida in Orlando.

Dr. Dietrich, thanks for being here today.

Dr. Dietrich:
Thank you so much for having me.

Dr. Turck:
Well, to start us off, Dr. Dietrich, would you walk us through how the treatment landscape for early-stage non-small cell lung cancer has evolved over the past decade, especially with increasing emphasis on perioperative strategies?

Dr. Dietrich:
Absolutely. The traditional cornerstone of curative intent surgery was really unchanged for several decades. We've used adjuvant chemotherapy. We didn't think about chemotherapy in and of itself as being very effective. Neoadjuvant approaches weren't really commonly done; we didn't think of them as impactful enough to really delay surgery. Cases that were deemed unresectable were typically referred to radiation treatment with chemotherapy.

This has evolved quite a bit. We've first seen the introduction of adjuvant immunotherapy post-chemotherapy—so a sequence of surgery followed by chemotherapy, and then immunotherapy—but we've had mixed results. We had two studies: IMpower010, which was very PD-L1 dependent, and then the PEARLS study with pembrolizumab, which gave us basically an across-the-board blurry result that was very hard to interpret. So we weren't really satisfied with what the adjuvant immunotherapy provided. I'll talk about where this could be useful later.

But we've gotten a shockwave and seen what chemoimmunotherapy in the neoadjuvant setting can do. And I think one of the strategies that we utilized here was first in CheckMate 816—three cycles of chemotherapy, histology-adjusted, plus the addition of immunotherapy with nivolumab. What we've seen is that one in four patients here developed not only very good responses on a clinical radiographic level, but even more importantly, on a pathological level. So we introduced pathological complete response—something that we would've never expected. We saw a few of those in the low one digits from chemotherapy alone, so there may be a subset that's very chemotherapy sensitive that's hard to identify, but there's exponentially higher pathological complete responses. And what was very nice to see, and that's an analogy to all the other cancers that we're treating, is that these pathological responses—and to a certain extent, major pathological responses—really predicted positive outcomes.

I think we used the tumor site here as a gauge of response for micrometastatic disease as well. That's typically the source of recurrence. So this has really changed, and we're really trying to move into the direction of chemoimmunotherapy, not only because we think of it as effective, but we also learn so much along the way. We learn whether or not an escalation is necessary and whether a

possible deescalation in the adjuvant setting is possible. And we also have seen that the surgeries are actually less extensive, so we've had less pneumonectomies and less bilobectomies. So this was an improvement in the right direction, across the board.

We've seen similar trials that use the perioperative approach, and we have multiple agents here. Nivolumab, certainly, in both settings—both neoadjuvant and perioperative—is available. We have them for durvalumab and for pembrolizumab as well. So this is really a strategy shift that, in all honesty, has been late in lung cancer. We've been doing this for breast cancer, gastroesophageal cancer, and bladder cancer. We used a systemic therapy in the neoadjuvant setting first and then proceeded with surgery. In lung cancer, again, we didn't have the effective combinations, which has now changed, and so the entire approach to early-stage resectable lung cancer has changed along with it.

Dr. Turck:
Since we're hearing more and more these days about perioperative therapy, I wanted to ask about its underlying rationale here. What else can you tell us about the key biological and clinical advantages of introducing immunotherapy before surgery as part of the perioperative strategy?

Dr. Dietrich:
I think there are two pillars. One is biological rationale, and the idea that the lymphocytes that have been exposed to tumor antigens are present—that's a very important part. This is a T-cell tumor cell interaction that we are stimulating with immunotherapy, and immunotherapy is clearly the main driver of efficacy here. And removing this first really removes the training ground for T lymphocytes to train for an anti-tumor response. That's the biological side.

The clinical side is that we learn a lot along the way. We may be downstaging these tumors as well, and not only having better immunotherapy responses, but also having better surgical outcomes with these patients. I think this is pretty consistent across the different trials; we're able to facilitate surgery in a way and improve long-term outcomes at the same time. Again, there will be, in the future, an opportunity—and we're certainly investigating this in clinical trials—to see if a patient who did not achieve a pCR or who may have persistent ctDNA with a pCR is going to have escalation opportunities where we don't continue with immunotherapy alone, and where we may add a mechanistically complementary antibody drug conjugate or maybe a combination immunotherapy. I think those are all opportunities, but establishing the sensitivity upfront is a huge opportunity for us to learn about the tumor's responsiveness and then help the patient get the appropriate adaptation of their treatment in the adjuvant setting.

Dr. Turck:
Building on that, what else can you tell us about how perioperative regimens are structured in practice and how they integrate neoadjuvant and adjuvant therapy within the broader clinical pathway?

Dr. Dietrich:
I can only speak for our practice, but I think this is a shift that happens across the field, maybe varying by geography. The adjuvant use of chemotherapy and immunotherapy is really based on the biological rationale we discussed and is a second preference for us. If a patient is upstaged during surgery, we may have a radiographic and preoperative evaluation that is consistent with stage one disease. But then, if we do a more comprehensive surgery, and all of a sudden, we find positive lymph nodes in the mediastinum, then yes, we give adjuvant chemotherapy and adjuvant immunotherapy like we used to. I think that's still happening. This is certainly a less common opportunity, but these incidental upstagings still suggest that the adjuvant pathway is a reasonable way.

But what we really try to do is get the staging right from the get-go. We like to do PET scans, EBUS evaluations, and an MRI of the brain for patients with stage two, stage three disease. And for those, it's clear that chemoimmunotherapy really provides an opportunity along the way of improving outcomes that we really didn't see in the same consistency with adjuvant immunotherapy. And adjuvant immunotherapy is a very nuanced discussion where biomarkers are a critical factor. I really think that the PEARLS study is the one outlier where we didn't see a correlation between response and PD-L1 level, and IMpower010 is very clear. The subset that really benefited was 50 percent or higher. We really think of even the lower PD-L1 levels as benefiting from the chemo immunotherapy in the neoadjuvant setting.

So I think if a patient is resectable, that doesn't necessarily mean that they should go straight to surgery. We'll have to make sure that we use our agents, and that we use them in the best possible sequence. And chemoimmunotherapy upfront really has been crystallized out as the way to go for many of these patients, even when they're upfront resectable.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Martin Dietrich about perioperative immunotherapy regimens for resectable non-small cell lung cancer.

So, Dr. Dietrich, when we're implementing perioperative regimens, what are some of the key operational considerations we should keep in mind around treatment sequencing, like you were discussing just before—timing of surgery and multidisciplinary coordination?

Dr. Dietrich:
The first step is the patient should see all providers upfront. I think it's critical in a multidisciplinary setting to see a medical and radiation oncologist, a thoracic oncologist, and a surgical oncologist at the very beginning. We get the full workup and interventional pulmonary workup with an EBUS, PET scan, MRI, and then, most importantly, molecular testing. If we have an EGFR or ALK mutation, we really don't want to subject them to immunotherapy. We know it's not working; we basically provide the patient only the benefit of chemotherapy, but all the side effects and cost associated with immunotherapy. So this is a different paradigm for those molecular subsets that has been worked out. We have targeted therapy here in the adjuvant setting. I think that's quite helpful.

Then, a relatively quick start; we decide on a patient's treatment course. I think it's oftentimes very feasible to start chemoimmunotherapy within two to three weeks after the original diagnosis after completing all the remainder of the workup.

And then it's really only nine weeks of treatment—week zero, week three, week six, and week nine—and the patient gets another follow-up scan when they complete all four cycles. And it's typically just a CT. We see activation of the lymph nodes by immunotherapy; we may see some inflammatory activity in the tumor that's related to immunotherapy. So PET scans are very difficult to evaluate in that context after early immunotherapy exposure.

And then we get the patient to surgery. In the clinical trials, we had up to six weeks. In my practice, it may be dependent on how well the patient tolerated therapy and how quickly they recover, so we're typically shooting for four weeks. I'm trying to get this done as early as possible. But the idea of getting the patient started on treatment, containing micrometastatic disease, and shrinking disease is really a primary objective of getting the patient the best treatment. The immunotherapy's effectiveness with the present tumor microenvironment being perceived to be best is certainly another reason. And then afterwards, when the patient has recovered from surgery, we are starting radiographic surveillance and maintenance immunotherapy.

I do have to say that if I compare across the different trials, and even, in particular, the CheckMate 816 neoadjuvant versus perioperative trials, I do think that the neoadjuvant portion is more valuable. That doesn't mean that the adjuvant portion doesn't carry a value; some patients may need more PD-1 stimulation for a sustained response. But I think the neoadjuvant portion really has made the biggest difference for us in terms of outcomes improvement and surgical strategies.

Dr. Turck:
One of the unique aspects of neoadjuvant therapy is that it gives us a chance to evaluate pathologic response after surgery. From your perspective, what insights does that response provide once surgery is completed?

Dr. Dietrich:
Pathological complete response is a critical factor for us because it serves as a surrogate marker of how well the patient responded to therapy and how micrometastatic disease as the source of metastatic recurrence has responded. So I don't really worry about it per se because it would've been cut out anyway. But it gives us a very good idea of how a disease that has escaped, and we know that 60 percent of these patients do recur, so we get a very good gauge how the response is.

In my practice, we do complement it with ctDNA. That's an evolving field. We want to see the clearance from the blood and the tissue; that's ideal. But pCR is a well-established marker and, in my opinion, should be an accepted surrogate endpoint for excellent outcomes, and maybe a surrogate endpoint for approvable clinical trials as well.

Dr. Turck:
Before we close, Dr. Dietrich, let's look ahead to emerging administration options. How might subcutaneous immunotherapy influence the overall patient experience as well as clinical workflow?

Dr. Dietrich:
One thing that we've learned from pharmacokinetics is that the PD-1 blockade has to be ongoing and durable. But the half-life of these antibodies is so long that peak concentrations probably don't play as much of a role, so we have learned over time that we can extend intervals. We give these regimens every three weeks in the beginning with immunotherapy because they're aligned to chemotherapy. We don't want the patient to have an extra visit, and the way to deliver it can be done based on the pharmacokinetics, either intravenously or subcutaneously.

The subcutaneous application obviously is much easier for the patient, it's much quicker, and, especially when they come for the adjuvant portion, the workflow is going to be much more straightforward. Those are simple applications that are done within a matter of five minutes as opposed to having to access a port or having to put in a peripheral IV. So the patients can get their treatment delivered

much faster, and then they essentially go on their way, but with the same efficacy; there's no difference. This takes pressure off the patient, but it also takes pressure off our nurses in infusion areas, who are always very busy. There's a significant shortage that we're experiencing. And so for us, making processes more efficient and fast for patients and giving as much time back as possible is a critical factor.

So what we've done for all patients in the adjuvant setting is we've moved to subcutaneous, and in the neoadjuvant setting, it's a case-by-case decision. Most patients prefer the faster application of the subcutaneous. There's no reason why we can't do it, but if we have to access the port, the time savings are probably not as significant in the neoadjuvant portion. But after surgery, it's subcutaneous only.

Dr. Turck:
With those forward-looking comments in mind, I want to thank my guest, Dr. Martin Dietrich, for joining me to review the evolution and integration of perioperative treatment approaches in early-stage non-small cell lung cancer.

Dr. Dietrich, it was wonderful having you on the program.

Dr. Dietrich:
It was a pleasure, thank you so much.

Announcer:
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