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Case Study: Treatment Sequencing in Platinum-Resistant Relapse ES-SCLC

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Dr. Sands:
My name is Dr. Jacob Sands. I'm a Thoracic Medical Oncologist at the Dana Farber Cancer Institute. And I'm very happy to be joined by Dr. Leal.

Dr. Leal:
Thank you. Thank you for the invitation. I look forward to our discussion.

Dr. Sands:
So, we'll start out with treatment sequencing in platinum-resistant extensive-stage small cell lung cancer. And we'll start out with a clinical case. So first of all, 68-year-old man with a past medical history of COPD, which of course is common, 50-pack-year smoking history, quit 10 years ago, presented to primary with an increasing cough. The workup essentially shows a lung mass, and CT scan with metastatic disease to the adrenal, liver, and bone. So multiple sites, extensive-stage small cell lung cancer. No involvement in the brain; MRI brain was clear.

Initially started treatment with carboplatin, etoposide, and atezolizumab. Of course, durvalumab is also approved in that setting. In this case, atezolizumab for 4 cycles of concurrent chemo and atezolizumab, and then followed by atezolizumab maintenance. About 5 months into treatment, scans unfortunately showed progression.

So, what to do in this scenario? Well, when we look to the NCCN guidelines, we get really a nice structure showing the various treatment options. And I'll point out just very briefly at the top is the greater than 6-month chemotherapy-free interval. And that is a little bit different than the less than 6-month, and our patient is the less than 6-month. The approved therapy in this setting is of course topotecan or lurbinectedin, both of which have FDA approval, and we'll talk about those. Other commonly used drugs are irinotecan, especially, and you see that highlighted in the preferred regimens. As far as other lines of consideration for therapy that we will end up discussing, there are others. So, I mentioned lurbinectedin, I mentioned topotecan and irinotecan, each of those in that top part. Re-treatment with platinum/etoposide is generally more considered in the U.S. for those with a chemotherapy-free interval greater than 6 months, but the guidelines support greater than 3 if desired. Nivolumab or pembrolizumab is only relevant in individuals who never got a checkpoint inhibitor, so not relevant to this patient. But something that I think is very important to consider in someone who had not previously gotten that. That would generally be someone who got chemo and radiation for limited-stage disease that now has extensive-stage. And so, in that case, you'd need to consider that. Paclitaxel, another line of therapy. And then just under that actually, temozolomide is something specifically in individuals with brain mets and prior radiation, where you now really need a drug with CNS penetration, and temozolomide does have good CNS penetration.

So first of all, historically, in the second-line setting topotecan has been our long-standing FDA approved drug. And on the right there, was the initial study that led to FDA approval. You can see it really overlapped quite a bit with CAV. So not really a superior outcome, but very similar outcome and was better tolerated than CAV, and that led to FDA approval. On the left side there, we see topotecan versus best supportive care. So, it beat best supportive care, but not the kind of separation of curves we'd want to see when the control arm is really not getting a line of therapy. And in PO, we do see some more GI toxicities.

And related to that, here is the toxicity profile of topotecan as PO or IV, and this is dosed day 1 to 5. So, this has been unfortunately a somewhat toxic regimen, particularly with cytopenias, some fatigue, GI toxicities, especially when it's a PO form, and then of course day 1 to 5. So, in the IV form, they're in the infusion room for 5 days.

Irinotecan is a commonly used alternative to topotecan, so some centers prefer irinotecan. I personally use irinotecan more than topotecan because of the toxicity profile. And here you see the data from irinotecan is really quite old. And looking at these older publications, the data is often presented in a more simplified form and often with fewer patients. This is a publication from 1992, so it was only 15 patients with a meaningful-appearing partial response, again under - with a small number of patients and median duration of only 58 days, but well tolerated.

Lurbinectedin in the second-line setting is a newer approved option. This is a once-every-3-week dosing, so its schedule is a bit better. But you'll see that the median progression-free survival, though, is something that still highlights the ongoing need for clinical trials and drug advances, the median progression-free survival of being 3.5 months. In this study, they split those between those who had progression - or their chemotherapy-free interval of less than 90 days, or more than 90 days. And not surprisingly, those with a longer chemotherapy-free interval did better. Still, median progression-free survival being 2.6 months or 4.6 months. I'll point out, though, that in the group that had a chemotherapy-free interval less than 90 days, 19% of them had ongoing disease control beyond 6 months. So that means their second-line therapy worked for longer than their first-line therapy in this difficult-to-treat disease, but it was only 19%. Whereas in the greater-than-90-day chemotherapy-free interval, that was about 44% of patients that had disease control beyond 6 months.

So, it's generally pretty well tolerated. And you see the swimmers plot here, with further demonstrating some of that durability. And then on the right side there is the toxicity profile. The neutropenia rate was pretty high, 46% having grade 3 or 4, but patients were not allowed to have primary prophylaxis. And so, in a patient that I'm treating where I'm particularly concerned about neutropenia, then I would give them some kind of prophylaxis. Although only 5% of patients in this study had febrile neutropenia. I'll point out that there was a 7% grade 3 fatigue. And so, I do think there are patients that unfortunately get very fatigued from this treatment, but generally, it's well tolerated.

Now paclitaxel is another treatment option. This is something that I tend to use further down. So, if I'm using lurbinectedin second line, then I'd use irinotecan third line, and paclitaxel would be more like my fourth-line choice. But other oncologists may order these a bit differently. I find paclitaxel, particularly with weekly dosing, is very well tolerated and also something that provides efficacy.

You know, each of these drugs is something that, realistically, there will be outliers. But generally, when they work, they're working for months. So again, highlighting the ongoing need for trials.

Now I mentioned nivolumab and pembrolizumab. And this is why I think this is so important to discuss is this was third-line pembrolizumab, so a 19% response rate with 13% ongoing disease control at 2 years, you see 17% at 1 year. So, the response rate is not high, but amongst those who have a response, the durability is really tremendous. And we know these to generally be pretty well-tolerated drugs, as well. But now these, of course, moved into the first line. So again, I'll say in someone who had a checkpoint inhibitor in the first line, as is the standard of care for extensive-stage small cell lung cancer, I would not give further checkpoint inhibitor at progression.

So, going back to our 68-year-old man, he had the 5-month chemotherapy-free interval. So, in that setting, really giving lurbinectedin I had mentioned as a second-line option, topotecan or irinotecan is also a second-line option. When we're talking about a 7-month chemotherapy-free interval, this is now beyond the 6 months and within NCCN guidelines, re-treatment with platinum/etoposide is a more realistic option. I will admit that I personally still don't tend to do a lot of re-treatment with platinum/etoposide.

And part of that is from here. So, this was a trial looking at platinum/etoposide re-treatment versus topotecan. And we see that on the left there, the bottom left, the overall survival curves really completely overlap. Now the progression-free survival did look a bit better with the combination chemotherapy, so platinum/etoposide re-treatment got a median progression-free survival of 4.7 months versus the 2.7 from topotecan. And so, that does seem to offer a benefit. I'll point out on the right, though, in the forest plot that the really the poll on that was more so from those who had the 6-month chemotherapy-free interval, the 180 days. And the 90 to 180 days actually overlaps there you see. So, I think the real benefit in that is more at the 6 months.

And just to briefly mention lurbinectedin, this is small numbers, but in those with a greater than 180-day chemotherapy-free interval, we also tend to see longer efficacy from lurbinectedin.

So, in summary, I'd say clinical trials continue to be extremely important in the second-line setting. Lurbinectedin does represent a second-line option with a Q3-week dosing that's generally well tolerated. Topotecan also FDA approved, or irinotecan, what I consider to be a better tolerated option, are also legitimate second line. Paclitaxel is another one supported by NCCN guidelines. And temozolomide is one of those particularly when you're looking for something with CNS penetration in later lines of therapy.

So, Dr. Leal, I just raced through some of the options, but let's slow it down for a moment and discuss a bit now. Can you take us through just your general framework of how you think of second-line and beyond treatment for extensive stage small cell lung cancer?

Dr. Leal:
So, I think defining platinum resistance versus platinum sensitivity is something that is really important. Although the definitions, as you pointed out in the studies, versus what NCCN defines as sensitive, they do tend to differ. So, there isn't a clear consensus. But I agree with you that for the patients that have had prior platinum and have not had significant toxicities with their prior platinum and have a chemotherapeutic-free interval of 180 days or greater, I do consider rechallenge with platinum. And most, in those patients that for example, if they had limited stage and did not get IO with their limited-stage treatment with concurrent platinum/etoposide, I think this is an opportunity to rechallenge and use immunotherapy. So those are the patients that are most likely will do the platinum rechallenge strategy.

For patients that have platinum-resistant disease or patients that have had platinum-sensitive disease but had significant toxicities with their prior regimen, I will tend to use lurbinectedin as my second-line option. As you pointed out, lurbinectedin has been well tolerated. And certainly, at least anecdotally in my practice, I've had less cytopenias compared to topotecan. So, I tend to use lurbinectedin in that second-line and beyond setting for those selected patients.

Dr. Sands:
So, in the consideration of irinotecan or topotecan, which one do you generally prefer?

Dr. Leal:
Definitely irinotecan. I think overall, the experience with irinotecan, especially if given weekly, has definitely been better tolerated and I think has had activity that's been demonstrated in single-arm phase 2 studies. In addition, in another study that was actually investigating another agent, the irinotecan arm actually showed favorable safety and numerical improvement in terms of overall survival compared to topotecan, although this study was not powered to determine that. So, in my clinical practice, if patients are requiring next line of therapy, I've generally used irinotecan as a third-line option and used the weekly approach.

Dr. Sands:
All that being said, we clearly need further drug development, and there is a lot going on currently in drug development. And so, clinical trial enrollment and consideration for trials, again, I'll highlight at the end of this as an area of great attention and should really be considered as options for patients in this setting.

Dr. Leal:
I agree, for sure.

Dr. Sands:
Well, thank you, Dr. Leal, for your insights, and thank you for joining us for this discussion of second-line treatment of small cell lung cancer.

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