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

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Dr. Leal:
Hello, I'm Dr. Ticiana Leal. I'm an Associate Professor and Director of the Thoracic Medical Oncology Program at the Winship Cancer Institute of Emory University in Atlanta, Georgia. Joined with me today is Dr. Jacob Sands.

Dr. Sands:
Thanks so much. Happy to join you.

Dr. Leal:
And we'll be continuing our sequence of discussions regarding management of patients with small cell lung cancer. I'll highlight treatment sequencing options in platinum-sensitive relapsed extensive-stage small cell lung cancer.

So, let's start with a case. This is a 67-year-old man from my clinical practice with past medical history of hypertension, COPD, and hyperlipidemia, and a 45-pack-year smoking history who presented to the emergency room with cough and chest pain for one week. This patient has ECOG performance status of 1, and initial workup demonstrated a right lower opacity in the chest x-ray. Follow-up imaging included a CT chest that revealed a 4.6-cm right lower lobe mass with associated right hilar and mediastinal lymphadenopathy. Bloodwork was notable for anemia with a hemoglobin of 8.4. Otherwise, this patient had adequate renal and hepatic functions. He underwent a bronchoscopy and biopsy of a 4R mediastinal lymph node that revealed the diagnosis of small cell lung cancer. Brain MRI done for staging purposes was negative for metastatic disease.

So, this patient underwent additional imaging, which included a PET/CT, and as is shown here, the PET/CT demonstrated the right lower lobe mass, hilar and mediastinal lymphadenopathy, as well as bone metastasis as is shown in the third box and also the first one. So now he's presenting to your medical oncology clinic to discuss first management of his diagnosis of extensive-stage small cell lung cancer.

So, in our case, this patient initiated standard-of-care therapy with platinum/etoposide plus durvalumab, a PD-L1 inhibitor. He completed 4 cycles of induction chemoimmunotherapy but had delays in initiating cycles 3 and 4 because of delayed count recovery. He then went on to receive durvalumab maintenance and did well until restaging CT scans after 7 cycles of maintenance durvalumab demonstrated multiple new and progressive hepatic lesions. His ECOG performance status remains preserved, and he wants to discuss next line of therapy.

So going back to the NCCN guidelines, which we frequently use in clinical practice to guide our next steps in clinical management and therapeutic decision-making, here's what we currently have. As preferred regimens for patients that have chemotherapy-free interval of greater than 6 months, clinical trial enrollment, as well as re-treatment with platinum-based doublet. However, the current FDA approvals

that we have for second line and beyond include topotecan, which is actually approved since 1996, and is really approved for patients with platinum-sensitive disease, who had progression of their disease at least 60 days after first-line chemotherapy. And lurbinectedin which had accelerated approval in June of 2020 for patients with metastatic small cell lung cancer, with disease progression on or after platinum-based chemotherapy, and there is no mention in the FDA approval regarding platinum-sensitive or platinum-resistant disease.

But as you can see here, there are multiple other regimens that can be considered, a lot of them really have been based on phase 2 single-arm trials. And of note, there is no approved third-line option in patients with small cell lung cancer in third line and beyond.

So, we've seen the results of the topotecan studies. We've seen here that topotecan has now been demonstrated to have efficacy in patients with small cell lung cancer based on two studies. The first one, as you can see here, is topotecan that was given versus best supportive care. And I want to point out that in this study, the median overall survival for patients on the topotecan arm was about 6 months. On the right, we're seeing another study that also demonstrated that topotecan versus CAV showed similar overall survival results, just to summarize the data, but had less toxicities and greater improvement in symptom control.

So, these were the studies that led to the approval and established use of topotecan in second line for patients with extensive-stage small cell lung cancer, of note, in patients that had a chemotherapy-free interval of at least 60 days after their frontline therapy. And this is obviously, you know, studies that were done when we did not have immunotherapy.

And the safety we've also seen, the main toxicities here with topotecan have really been myelosuppression. And I think this is something that mirrors what we see in clinical practice and is a significant clinical challenge in use of topotecan in second line.

And the data for platinum doublet rechallenge had been data that was really established from the 80s. A lot of them had been case series. But this was our first randomized phase 3 study establishing the potential benefit of using platinum doublet rechallenge versus topotecan. This is a randomized phase 3 study. The primary endpoint of progression-free survival did show an improvement in progression-free survival, with the use of platinum doublet rechallenge versus topotecan with a median PFS of 4.7 months versus 2.7 months with a hazard ratio of 0.57. But as is shown on the right, there is no significant overall survival benefit. And in fact, the median overall survival was almost numerically identical for both groups. And the toxicities were actually not that much different. As you can imagine, myelosuppression was the main toxicities that were seen in both arms. Of note, there was high rates of crossover in almost 40% in the topotecan group. However, I think this is the best data that we have, that really establishes the use of platinum doublet rechallenge in patients with platinum-sensitive disease.

So, our next study demonstrated here is investigating lurbinectedin. Lurbinectedin is a selective inhibitor of oncogenic transcription, and it may also have effect on the tumor microenvironment by inhibiting active transcription in tumor-associated macrophages and affecting the immune response with activation of immune checkpoints.

And the results of lurbinectedin that led to the approval of lurbinectedin in second-line small cell lung cancer based on this phase 2 BASKET trial that included multiple cohorts, focusing here on the patients with small cell lung cancer. Of note in the inclusion, they did allow patients with performance status of 0 to 2. However, only about 8% of patients had ECOG performance status of 2. They did allow prior immunotherapy; however, you know, because of when this study was conducted, immunotherapy was not well established in many sites in this global study, and only about 8% of patients had prior immunotherapy. Here, patients with CNS metastasis were also excluded. The primary endpoint of this study was overall response rate, and the primary endpoint was met.

I'd like to highlight the overall response rate of 35% in the patients defined as platinum sensitive which were defined as patients with chemotherapy-free interval of 90 days or greater. The overall response rate, not surprisingly, was improved of 45%, in the platinum-resistant population 22%. Now keep in mind in the topotecan studies, the overall response rate is generally less than 10%. With regards to PFS, we also saw favorable PFS here with a median PFS of 3.9 months. PFS in the sensitive population of 4.6 months, and in the resistant population of 2.6 months. Going on to median overall survival, the median overall survival here favorable, 9.3 months, in the sensitive population 11.9 months, and in the resistant population 5 months.

So, another interesting analysis that was done, exploratory in nature, was looking at the activity of lurbinectedin in patients with small cell lung cancer with a chemotherapy-free interval of 90 days or greater and 180 days or greater. And I'll point out here, I think the most meaningful endpoint in sort of the summary of this exploratory analysis, is the median overall survival. We're seeing here the median overall survival in this small subgroup of patients with a chemotherapy-free interval of 90 days or greater is 11.9 months. And then in the patients with chemotherapy-free interval of 180 days or greater, this is 16.2 months. Again, the numbers are small, but putting it into perspective, when we saw the randomized phase 3 trial that established platinum rechallenge, the median overall survival there was about 7.4 months.

And then moving on in terms of outcomes in patients assessed as responders. Again, here looking at the outcomes in terms of the overall survival at 12 months, in the overall population 54.3 months at the 12-month landmark analysis, at less than 90 days 40%, at the

90 days or greater 60%.

In terms of safety, I think overall the tolerability of lurbinectedin was demonstrated in this single-arm phase 2 BASKET trial. The main toxicities that we see are myelosuppression; however, in terms of neutropenia, we do see grades 3 and 4 of 21% and 25%, respectively, but the rates of neutropenic fever are quite low. Other alterations to monitor for are elevated creatinine, elevated AST/ALT, and fatigue that can be seen in grade 3 in 7% of patients. The majority of these side effects are manageable with dose hold and dose reductions, and about 20% of the patients did require growth factor support for neutropenia in this study.

Another interesting analysis now that was done of the phase 3 ATLANTIS trial. This was a randomized phase 3 study that included patients with one prior platinum chemotherapy line, PD-1/PD-L1 inhibitors were also permitted. And this was a study that randomized patients to doxorubicin plus lurbinectedin, using a lower dose at 2 mg/m^2, versus the standard of care which was topotecan or CAV. For the patients that continued on the combination strategy arm for 10 cycles or greater, they were then allowed to continue on therapy with monotherapy, given the cap on doxorubicin, given risk of cardiotoxicity. When patients went on to monotherapy after 10 cycles, they were allowed to dose escalate back up to lurbinectedin at 3.2 mg/m^2. And there were about 50 patients that were included in this exploratory analysis. On the right, we're seeing the baseline patient characteristics. And of note, as you can see, here, the majority of these patients had chemotherapy-free interval of 90 days or greater, or 180 days or greater. As you can see here, 96% of the patients had a chemotherapy-free interval of 90 days or greater. And what we saw was really encouraging responses in overall survival in this small subset exploratory analysis.

On the left, what we're seeing is that for the patients that had a response to lurbinectedin combination with doxorubicin, when they then went on to maintenance lurbinectedin, the patients that had a response tended to maintain the response. And there were small number of patients that actually had stable disease that then went on to have a partial response. And I'll highlight here in this exploratory analysis, the very promising median overall survival of 20.7 months in this patient population, the majority considered platinum sensitive.

So, let's go back to our patient. Our patient had platinum-sensitive disease. Let's remember that this patient did have significant cytopenias and delays with their initial frontline combination strategy with platinum/etoposide. This patient, we decided together to continue on second-line therapy with lurbinectedin. The patient did tolerate the treatment well; however, the patient was noted to have progression after 4 cycles of lurbinectedin with an increasing number of hepatic metastasis and enlarging mediastinal adenopathy. The patient remains with preserved performance status, and inquires about other treatment options.

One thing I'd like to highlight is, again, a lot of questions about how do we sequence the strategies? This was an exploratory analysis in patients that had platinum after lurbinectedin. This is a post hoc exploratory analysis, 105 patients were included, 60 patients had chemotherapy-free interval of 90 days or greater. And as you can see here, 44 patients received further therapy, and of these, 27 patients received platinum after lurbinectedin. And here, what it demonstrates is that patients that had further platinum, on the right, actually had a median overall survival of 15.9 months, which number one, I think demonstrates the feasibility ofsequencing those patients after lurbinectedin. And number two, I think demonstrating that there is here efficacy of using a platinum in these selected patients following lurbinectedin in third-line strategy.

So, in conclusion, treatment for patients with small cell lung cancer in the relapsed setting needs to be individualized. Platinum rechallenge is an option for patients with platinum-sensitive disease in the relapsed setting. However, there's no significant difference in overall survival compared to topotecan. Lurbinectedin as a single agent remains an option for salvage therapy, preferably in patients with platinum-sensitive disease, although there's also efficacy in patients with platinum-resistant disease as well.

Dr. Sands, tell me a little bit about your approach for the patients with platinum-sensitive disease and what factors would have made you and your patient make a decision on what option to choose in the second line?

Dr. Sands:
Yeah, so I think of it similarly. I would generally use lurbinectedin as my second-line therapy. I think irinotecan is another good option in lieu of topotecan, which I don't like as much because of the toxicity profile. Retreatment with platinum/etoposide is not generally my preference, at least in part from the toxicity profile. We expect to get less out of it as a next line than we did out of the first line.

That being said, I loved the data you showed at the end there in showing that you don't have to use platinum/etoposide re-treatment as a second line; that still is an option to consider down the line for patients that maintain their functional status and such. And so, I think it's important to highlight that as a real treatment option, particularly since we are limited in the number of options that we really have. But, but it's not really my preference in platinum retreatment.

Dr. Leal:
Great, thank you for your insights.

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