Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/case-study-sequencing-therapy-in-es-sclc-in-special-patient-populations/16487/

Released: 11/30/2023
Valid until: 11/30/2024
Time needed to complete: 1h 22m

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

Case Study: Sequencing Therapy in ES-SCLC in Special Patient Populations

Announcer Open:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

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. And today I'm joined by my colleague, Dr. Jacobs Sands, to discuss extensive-stage small cell lung cancer management and strategies.

Dr. Sands:
Very happy to join you. Thanks.

Dr. Leal:
So, today we'll talk about sequencing therapy in patients with extensive-stage small cell lung cancer, focusing on special patient populations.

So, let's start with a clinical case. This is a 62-year-old female, former smoker, who was initially diagnosed with limited-stage small cell lung cancer in 2021. She was treated with concurrent chemoradiation, with 4 cycles of cisplatin/etoposide, and prophylactic whole brain radiation, PCI. At follow-up, approximately 12 months after completion of platinum chemotherapy, PET/CT showed new retroperitoneal adenopathy and left adnexal mass. The retroperitoneal lymph node was biopsied and revealed recurrent metastatic small cell lung cancer with associated necrosis.

This patient was deemed to have platinum-sensitive disease and was initiated on therapy with carboplatin/etoposide, in combination with immunotherapy with a PD-L1 inhibitor, atezolizumab, for 4 cycles, followed by maintenance atezolizumab. CT scan 3 months after completion of the platinum chemotherapy showed an increase in size of the left adnexal mass, and also increase in size in the retroperitoneal lymph nodes. The patient remained well and continued to work full-time despite this progression, and is quite active. She presents now to the medical oncology clinic to discuss further management.

In addition, further staging, which included a brain MRI, did show two small brain metastases as is shown in the right, one in the right middle cranial fossa and another one in the left thalamus without significant edema. There was some mild edema, and the patient did not have any significant neurologic symptoms despite these findings. You can also see some mild associated mass effect.

So, let's think about the management of relapsed small cell lung cancer, going back to the NCCN guidelines. This is now a patient who has had platinum rechallenge. Based on her initial diagnosis of limited stage, being platinum sensitive with disease-free interval of about 12 months, she was rechallenged with platinum/etoposide, in combination with immunotherapy, which I think this was a good strategy at the time. However, you know, the benefit that she received with the platinum rechallenge was of shorter duration than her first time when she received it with limited-stage treatment.

We have other options here in second-line now for metastatic disease, which include topotecan, as well as lurbinectedin. And there are multiple other options that we're faced with discussing with the patient, what is the next best line of therapy for her.

Another important factor to consider is the presence now of intracranial metastasis. Although the patient is neurologically stable without any significant neurologic symptoms, we are seeing two new brain lesions with mild edema, mild mass effect, and certainly we do need to treat these lesions with the addition of immunotherapy to platinum/etoposide. In both IMpower133 that established the use of atezolizumab and chemotherapy, as well as in the CASPIAN study that established the use of durvalumab with chemotherapy, PCI was not allowed in the experimental arms. So, the full effect of immunotherapy and radiation in patients with small cell lung cancer, I think, is yet to be defined.

But I think this was an interesting and encouraging exploratory analysis that was performed and presented using the IMpower133 data. And what it showed is that patients in the IMpower133 that received atezo plus chemotherapy, versus placebo plus chemotherapy, had, you know, the median time to intracranial progression was longer, 20.2 months versus 10.5 months, with a hazard ratio 0.66. This is for descriptive purposes only, and was not statistically, you know, powered into the study.

In addition, we did see also from the CASPIAN data that patients derived benefit from durvalumab with chemotherapy regardless of whether or not they had brain metastases at baseline.

However, at this time, we don't treat, at least I don't treat in clinical practice, patients with small cell lung cancer with immunotherapy alone. And this patient, unfortunately, has already had whole brain radiation in the form of PCI. And this is a significant challenge that we face in clinical practice. Brain metastases are very common in patients with extensive-stage small cell lung cancer and can occur in up to 50% in the course of their disease. International guidelines and surveys on care patterns still regard whole brain radiation as a standard of care for the setting in clinical practice. And despite the continuous implementation of SRS, or stereotactic radiosurgery, for patients with limited number of brain metastases in very solid tumors, including non-small cell lung cancer, and despite the increasing evidence of neurocognitive toxicity from whole brain, patients with brain mets from small cell lung cancer are still considered typical candidates for whole brain radiation.

However, I think there's increasing interest in using stereotactic radiosurgery for patients with small cell lung cancer. There have been lots of single-arm studies demonstrating the potential efficacy, less toxicity for patients with small cell lung cancer with brain mets who receive SRS.

This is a nice meta-analysis that was performed demonstrating here that SRS was associated with longer survival compared with whole brain radiation, with or without SRS boost. And certainly, in this study, as in other studies that have been done, including the single-arm studies included here, this is also associated with less neurocognitive toxicity.

In addition, in patients with small cell lung cancer, a study on PCI with or without hippocampal avoidance has shown that at least partial sparing of the uninvolved brain can translate into improved preservation of cognition. And as we showed in our prior slide, in the meta-analysis, there was no significant reduction in overall survival when you use SRS compared with whole brain. And now there's an ongoing study called the ENCEPHALON trial that is investigating the potential cognitive benefit of SRS versus whole brain radiation in patients with small cell lung cancer.

Let's move on to other special populations. Certainly, small cell lung cancer is a disease of older patients that impacts older patients. Here is a post hoc analysis of efficacy and safety of lurbinectedin in patients with relapsed small cell lung cancer, 65 and older that were included in both the phase 2 BASKET trial, so 26 patients treated with lurbinectedin, and in the randomized phase 3 ATLANTIS trial, 121 patients that were treated with lurbinectedin plus doxorubicin and 118 patients treated in the control arm.

So, what we saw here, to summarize the data, is that in patients aged 65 and older, lurbinectedin compared favorably to standard of care in terms of both efficacy, so higher response rate and longer duration of response and overall survival, as well as safety, including, importantly, less association with hematologic adverse events, which reinforces that lurbinectedin can be an option for patients 65 and older.

Now, let's talk about real-world outcomes with lurbinectedin in the setting of managing patients with relapsed extensive-stage small cell lung cancer. This is an updated sort of contemporary analysis, in my opinion, of a study looking at patients in the second-line with extensive-stage small cell lung cancer. And I think it's important to note the inclusion of which patients were used in this real-world study, the median age here 67 years, 50% were female, and of these, 94% had de novo small cell lung cancer. And interestingly here, they included 6% of patients with small cell lung cancer transformation. So, a bit of a more heterogeneous population, as we don't know if the behavior of small cell transformation and response to therapy is the same as it would be for de novo small cell lung cancer. Most patients had ECOG performance status of 0 or 1, and 10% had ECOG performance status of 2. But it also included patients with ECOG performed status of 3, which were excluded from the single-arm phase 2 BASKET trial; 52% of the patients had chemotherapy-free

interval less than 90 days, and 54% of the patients had CNS metastasis prior to starting second-line lurbinectedin. All patients had previously received platinum-based chemotherapy and immunotherapy.

And I'll just highlight some differences from the phase 2 BASKET trial for lurbinectedin. And as you can see here, you know, we have 54% of patients with CNS mets, whereas in the lurbinectedin study, we only had 4% of patients with CNS mets. And here, all patients had received prior platinum-based chemotherapy and immunotherapy, whereas in the lurbinectedin study, only 8% of patients had prior immunotherapy. So, this is a real-world population. These are the patients that I think we really do see in clinical practice, and it does include more than half of the patients with platinum-refractory disease.

And here's what we saw in terms of the real-world data in terms of efficacy for patients who received lurbinectedin second-line for extensive-stage small cell lung cancer. The median progression-free survival that is seen on the left is a median PFS of 2.1 months. The median overall survival in this real-world study is 5.1 months. And what we're seeing on the far right, is that they're doing the overall survival based on the chemotherapy-free interval. And although it wasn't statistically significant, there was a numerical improvement in median PFS in patients that had a chemotherapy-free interval of 90 days or greater, versus less than 90 days. And in addition, there was also a numerical improvement in overall survival according to the chemotherapy-free interval, with slightly larger improvement numerically of median overall survival in the population of patients who had a chemotherapy-free interval of 90 days or greater. We see a median overall survival of 7.8 months in the chemotherapy-free interval of 90 days or greater, versus 4.4 months in patients with a chemotherapy-free interval of less than 90 days.

In this study, lurbinectedin was generally well tolerated. According to what we saw here, which mirrors what we saw in the phase 2 BASKET trial, the most common adverse events included neutropenia, anemia, and fatigue. Febrile neutropenia was consistent with what was found in the phase 2 BASKET trial, and the rate of growth factor administration was similar to that in the trial, 22%. Importantly, no patients discontinued lurbinectedin therapy due to treatment-related adverse events, and there were no grade 5 toxicities seen in this real-world study.

Moving on to another dataset now, from a European dataset, looking at the real-world outcomes for patients with lurbinectedin in the second-line setting for extensive-stage small cell lung cancer. Here, the median progression-free survival was 1.9 months. And again, here we're seeing numerical improvement, according to chemotherapy-free interval of 90 days or greater, which was 2.4 months versus in the less than 90 days, 1.5 months. And in a multivariate analysis, only chemotherapy-free interval of 90 days or greater was significantly associated with more prolonged progression-free survival. In addition, they also looked and reported at overall survival, the median overall survival in the overall cohort was 4.7 months, the median overall survival according to chemotherapy-free interval 6.5 months in the 90 days or greater, 3.7 months in less than 90 days. In a multivariate analysis, only performance status and chemotherapy-free interval of 90 days or greater, were significantly associated with more prolonged overall survival.

And this is now looking at the real-world PFS for the overall second-line lurbinectedin monotherapy population in subsets looking at chemotherapy-free interval of 90 days or greater and 180 days or greater. The mean real-world PFS in the overall population was 2.5 months. When you look at the chemotherapy-free interval of 90 days or greater, that's 3.1 months, 180 days or greater 4.6 months. Of note, 85% of the patients received immunotherapy in combination with platinum therapy in the first-line setting, 27% of the patients had a recorded third-line treatment after their second-line lurbinectedin, and 288 patients did not receive subsequent therapy. And I think, you know, this is important to highlight that decision for second-line, because I think as we discussed previously, you really do see a big drop off in the number of patients that are able to receive third-line therapy.

So, for our patient, let's go back and remember our case, this is a patient who had already received platinum/etoposide/atezo in the rechallenge setting, went on to receive lurbinectedin. But I think we also needed to address the issue of the recurrence in the brain in somebody who had prior PCI, and certainly this is a data-free zone. But the option of whole brain radiation is also significantly associated with toxicity and unknown efficacy. So, in the case of our patient, extrapolating from the data that we have from single-arm phase 2 studies as well as the meta-analysis, she underwent SRS to the two brain lesions and tolerated treatment well. She then initiated therapy with lurbinectedin and derived clinical benefit.

So, in conclusion, treatment for patients with small cell lung cancer in the relapsed setting needs to be individualized. In patients with small cell lung cancer, a study on PCI with or without hippocampal avoidance has shown that at least partial sparing of the uninvolved brain can translate into improved preservation of cognition. In a meta-analysis, there was no significant reduction in overall survival associated with SRS compared with whole brain. The ENCEPHALON trial is investigating the potential cognitive benefit of SRS versus whole brain in patients with small cell. And real-world treatment results and outcomes have shown that lurbinectedin is generally well tolerated.

So, reviewing specific patient populations that we treat in clinical practice, you know, small cell lung cancer is a disease of older patients, because of comorbidities and high burden of disease, many patients present with ECOG performance status of 2 or 3,

especially in second-line. Tell me your insights and how you manage patients that are older, older than 65, and patients with poor performance status.

Dr. Sands:
Well, poor performance status is tough. I mean, I think the question in those cases I wonder about is, is their poor performance status due to their disease, or due to comorbidities? So, in someone who has had rapid progression of their disease and poor performance status because of symptoms from small cell lung cancer, that is something that has acutely occurred over the last, you know, over the prior couple of weeks or something, that's one thing, versus someone who has multiple comorbidities and long-standing weakness and has been using a wheelchair to get around distances for the longer-term.

In the latter, where it's a more long-standing poor performance status, I'm more hesitant about further treatment in those patients as you get to later lines of therapy. In someone who has been active, but now has limitations because of symptoms related to progression, whether that be pain or some other aspect, then I will consider treating them.

And you know, age, I've treated some patients that are pretty far along and, you know, even into early 90s, in someone who is extremely active, I mean, we're talking about, you know, someone who's more active than the average 80-year-old, then by age alone it's not really off the table, but we have really direct discussions about that. But I'm more hesitant as patients get older, but I don't really have a limit to that.

Now, as far as, you know, fitting this special population, though, for brain mets, where someone has brain mets, and they've gotten prior radiation to their brain, and so then I'm thinking about what systemic therapies in that setting, especially as we get to the later lines of therapy, temozolomide is something that I may then reach for, rather than like paclitaxel, for example. Lurbinectedin, there's not really data for brain. I have had one patient, incidentally, that did have response, intracranial response, but it's not something I expect. And so, lurbinectedin would not really be a choice. Irinotecan or topotecan have some CNS penetration and also would be options in those cases. Although in someone who's got progression in the brain and needing systemic therapy to control that, I mean, that is a - that's a terrible scenario. I mean, so we have very direct discussions about that. And realistically, when these therapies work, these systemic therapies work for that, it's for a limited number of months. Now, there can be outliers, and we always hope for that. But those are the drugs I would choose based upon trying to control intracranial disease.

Dr. Leal:
Yeah, definitely. I definitely agree with that approach. And that is a similar approach we take here. Thanks so much for your insights on this case.

Announcer Close:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, LLC. and is part of our MinuteCE curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.