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

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Case Study: Managing Common Adverse Events Associated with Second-Line Treatment of ES-SCLC

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Dr. Sands:
Welcome back to our discussion on small cell lung cancer. I'm Dr. Jacob Sands, Thoracic Medical Oncologist from Dana Farber Cancer Institute. And joining me today is Dr. Ticiana Leal from Winship at Emory.

Dr. Leal:
Thank you. Thank you for the invite. Look forward to our discussion.

Dr. Sands:
So, we're going to discuss - this one is managing common adverse events associated with second-line treatment of extensive-stage small cell lung cancer. And we'll start out with a case, 62-year-old nurse with approximately 45-pack-year smoking history presented to the emergency room with right chest wall pain.

And I'll pause briefly just to point out that all of these cases that we're discussing across each of these episodes really qualify for lung screening. Now, these patients are not typically diagnosed by lung screening, because the rates of lung screening are so low. But I just want to make sure people keep that in mind, because it is an important aspect of trying to catch this earlier.

But this patient presented with right chest wall pain, had a workup. There was no PE. Of course, that was the first thing looking at in the emergency room. But there was disease noted on the scan. And this did involve the liver. And ultimately ended up getting a PET scan. And you can see there on the right is that the disease throughout the liver was quite extensive.

The patient was started on carboplatin, etoposide, and atezolizumab as first-line therapy, and really had a near-complete response on treatment, but about a year into the maintenance atezolizumab, had worsening anemia. And so, we'll come back to that in a moment.

But let's start out then with talking about some of the toxicities related to checkpoint inhibitors. Now when I talk to patients, I'll highlight that the mechanism of action of checkpoint inhibitors is not to actively kill their cancer but rather to help their immune systems recognize the cancer so that their immune systems actually kill the cancer. And patients find that quite appealing actually that their immune system can do that. But we talk about that the side effects then can be related to inflammation from their immune system in areas that we don't want it. I specifically highlight the common ones, skin, rash, the colon, terrible diarrhea, and we talk about these others, but they're less common. So, myocarditis, pneumonitis, of course, is one to highlight. Adrenal insufficiency is one to really be aware of, because it's not always so apparent but something that needs to be thought of. Also, autoimmune diabetes, patients can get a type 1 diabetes, again, not common, but when it occurs, is obviously very important to catch. And so, this is, here on this figure, you see an array of these different toxicities that can come from checkpoint inhibitors.

And the time-course of these can be a little bit different. Now, of course, they can occur outside of these defined time-courses. But this gives a little bit of a timeframes of when it's more common, to really consider it.

Now in our patient, I mentioned that near-complete response. And you can see there on the right, 2 months into treatment, on a CAT scan her liver really looked dramatically better. And now is about 3 years since starting treatment. And you can see her disease is really extremely limited in volume. But that anemia on further workup ended up having a pure red cell aplasia. So, she was started on prednisone, but unfortunately did not have a lot of improvement, and then ultimately treated with IVIG and maintained on a long steroid taper. And with that, did have resolution of anemia. Now, I'll admit this was with the assistance of hematology. So, I had done some workup, but upon recognizing this red cell aplasia, then referred her over to hematology to include them with the diagnosis and then ultimately the treatment.

Now going to the toxicities of platinum re-treatment or topotecan, so separately now this is in the second-line setting. We see neutropenia really quite common, febrile neutropenia occurring for some. And in the topotecan arm there you see a cumulative 13% with febrile neutropenia, about 6% in the platinum/etoposide re-treatment, and nausea and vomiting can occur in both.

Now looking at including lurbinectedin in that discussion, you see neutropenia also quite common with lurbinectedin. About 5% febrile neutropenia with lurbi. And we've previously discussed in the other episodes the fatigue that can occur from lurbinectedin. And looking over at the comparison then with topotecan, again we've mentioned the cytopenias and certainly fatigue. PO type topotecan also does include more GI toxicities as well.

And on a prior episode we talked about the ATLANTIS trial of lurbinectedin plus doxorubicin. This was versus topotecan or CAV. And overall was a negative trial in that the curves really overlap. Similarly, you'll see on the left side, the duration of response does seem to be a bit better with the lurbinectedin plus doxorubicin, and Dr. Leal did a really nice job outlining, especially the tail of that curve in a prior episode.

But looking at the toxicity profiles now, we see on the left there is just the lurbinectedin alone. And in the middle there is lurbinectedin monotherapy on the ATLANTIS trial. And so, with that, we see a 4% febrile neutropenia, so that rate really stands up the 4 to 5%. So low febrile neutropenia. And on the right there you see the ATLANTIS trial, lurbinectedin plus doxorubicin, in the middle, they're still maintained only about 5% febrile neutropenia, that was a little over 9% with the topotecan or CAV. Fatigue levels, somewhat similar, maybe numerically a little bit more. And neutropenia really quite common across all of these.

Now, filgrastim or pegfilgrastim, this is, you see on the bottom there, is the comparisons. And so pegfilgrastim is really commonly utilized. ASCO guidelines recommend the use of prophylaxis for individuals or settings where the risk of febrile neutropenia is at least 20%. And so that's common practice. Now, that being said, in a certain setting, such as lurbinectedin, where the risk of febrile neutropenia is considered substantially less than that, but if I have a patient where I'm particularly concerned about neutropenia or the risk of neutropenia, then I will use pegfilgrastim in that setting. But it's not standard practice for me in that, in lurbinectedin, because of that lower rate.

Now, another option is trilaciclib. And this is a prophylaxis that's approved given with platinum/etoposide or topotecan. This is a transient and reversible inhibitor of CK4 and 6. And has really demonstrated decreasing or less incidence of anemia, thrombocytopenia, and neutropenia. So, it's helping protect all cell lines. It's given prior to infusion. And one aspect of the publications that I really appreciated is particular attention to the quality of life. And so, on the left side here, you see that in each of these, patients did better with the trilaciclib than they did with the placebo. So overall well-being, functional wellbeing, and fatigue was improved with trilaciclib. And so, on the right you see less transfusions and such.

But I think one of the big takeaways for me on this is that we are likely underappreciating how much anemia is impacting fatigue, and I think we think of well, our treatments cause fatigue and so there can be some element of fatigue, that doesn't necessarily raise our attention to do something. The anemia, not necessarily being so much that we would transfuse, but might actually really be affecting patients' fatigue levels as well. And so, I've been more attentive.

Now I don't use trilaciclib for everybody, but I have found that in patients where their platelet counts are not holding up or their hemoglobin is not holding up, it has worked remarkably well for those settings. And of course, it helps with neutropenia as well. And so, if I am going to treat somebody with prophylaxis to prevent neutropenia, it is also a consideration then that trilaciclib would be something that helps protect other cell lines as well.

Now, other regimens that I think are well tolerated, which we've discussed in prior episodes with irinotecan, I dose that day 1, day 8. And paclitaxel, I'll do the weekly dosing, 6 on, 2 off, because those are just generally better tolerated.

Now also to mention early palliative care for small cell lung cancer has also been shown to improve outcomes. And you see on the right

there, even though surviving to end up with early palliative care has improved survival, and then it certainly with symptoms has improved outcomes.

So, to summarize, checkpoint inhibitors have a unique toxicity profile. Cytopenias are common adverse events when treating with cytotoxic therapy. Pegfilgrastim is an effective way at reducing the duration of neutropenia, as well as preventing some of the complications from it. Trilaciclib helps with all cell lines, has also demonstrated improvement in health-related quality of life.

And palliative care is an important consideration for patients when they're getting into later lines of therapy. I'll say I find who to see palliative care is not something where I just have everybody see them, but I am more attentive to patients that I think can really benefit from that and have a low threshold for incorporating palliative care.

So, Dr. Leal, let's start out then looking at - we've gone over the toxicity profile of lurbinectedin quite a bit. Can you discuss, though, your management of some of those toxicities? Is there anything that sticks out for you? And how do you manage it? And also, as part of that, the cytopenias, as we've discussed, the neutropenia is quite common, although neutropenic fever is low, and is that a concern of yours?

Dr. Leal:
Yeah, definitely. I think, you know, overall, my clinical experience managing side effects of lurbinectedin mirrors what we saw in the phase 2 study. Myelosuppression is the most common, and typically mild anemia, thrombocytopenia, mostly grade 1 and 2 is what I've seen. The neutropenia has not been something that I've really encountered a whole lot. But I will say that in the patients that I did, if they were having neutropenia only as a side effect, I tended to add growth factor support, if they were otherwise tolerating the treatment without any other cytopenias or other side effects, and having good response to therapy, and overall having clinical benefit.

For the patients that I did have fatigue as a significant side effect, what really helped was dose hold and dose reductions. So, I think all the side effects that I've encountered have been manageable. Dose holds and dose reductions have been very effective, especially for the patients that have persistent fatigue and are on more prolonged therapy.

I haven't encountered a whole lot of neutropenic fever, kind of marrying, I think, perhaps even less than what we saw in the study. So overall, I think even in patients that are older, it has been a strategy that I've found manageable to sort of work with patients.

Dr. Sands:
Dr. Leal, maybe just to focus on one question for you, because it does seem to vary. But trilaciclib, is this something that you're utilizing in your practice? Are there specific patients that you're identifying for this? Or what's your experience?

Dr. Leal:
Trilaciclib is an interesting agent. We do have FDA approval for it as a myelo-protective agent in combination of platinum/etoposide plus/minus IO and in combination with topotecan. I have used it in selected patients. And I try to individualize the approach on who I will utilize trilaciclib in.

The clinical scenarios that I've found it most helpful are in patients that I'm rechallenging that patient that I discussed that had limited stage, and I'm rechallenging with a platinum/etoposide and IO, and they had significant cytopenias with their first course of platinum/etoposide, I have added trilaciclib. In addition, I've also added it in patients who are heavily pretreated. I don't use topotecan very often, but I've used it in situations where patients were very motivated to have a next line of therapy and it had sort of the common ones that I discussed that were my preferred agents. You know, this is a patient who had platinum/etoposide IO, lurbinectedin, irinotecan, paclitaxel, really wanted a next line of therapy, and I was really concerned about cytopenias, and so I did use trilaciclib.

So, I think it is a potentially valuable tool that we can individualize. It does add chair time. Overall trilaciclib has been well tolerated in patients that I've added it to chemotherapy. And currently, we're collaborating with Jared Weiss on a study investigating the use of trilaciclib with lurbinectedin, looking at similar endpoints as well.

Dr. Sands:
That's great. It sounds like we have a similar perspective on that, as well. So, we thank you, Dr. Leal, and thank you to our viewers for joining us for this episode on our discussion of small cell lung cancer.

Announcer Close:
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