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

Exploring Advances in Treatment: A Step Forward in Small Cell Lung Cancer

Dr. Sands:
Small cell lung cancer accounts for about 13 percent of lung cancer. Although often sensitive to first line treatment, resistant disease presents challenges at progression. Will recent and ongoing advances in the treatment landscape help us overcome that challenge? Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands and here to talk about the latest advances in small-cell lung cancer is Dr. Millie Das, a Clinical Associate Professor of Medical Oncology at Stanford University and Chief of Oncology at the Veteran's Affairs Palo Alto Healthcare System in California. Dr. Das, welcome to the program.

Dr. Das:
Thanks so much. It's, it's great to be here.

Dr. Sands:
To start us off, can you give us a better understanding of small cell lung cancer diagnostics? What do you look at in the pathology and also, can you discuss some of the staging with imaging and how that guides treatment decision making?

Dr. Das:
Absolutely. I think the diagnostics for small cell lung cancer is unique. This is a rare tumor that we see in the clinic, so many of us who specialize in thoracic oncology, the vast majority of our patients really have non-small cell lung cancer. And there are a number of different histologies that are represented within non-small cell. Small cell only represents about 10 to 15 percent of all lung cancers. It's really characterized as being more aggressive and unfortunately, a lot of the targeted therapies that have led to survival improvements in non-small cell lung cancer just really don't exist in small cell lung cancer. When we do diagnose a patient with small cell lung cancer, we often times are actually speaking to our pathologists about whether this is bonified small cell lung cancer or whether we're seeing any evidence of mixed histology or a large cell neuroendocrine tumor, which is under that neuroendocrine spectrum of malignancies. And so I think it's very important to figure out exactly what histology we're dealing with, which will help inform our treatment decisions and also can have some prognostic implications.

And then as far as the staging for small cell lung cancer, traditionally we think about TNM staging for solid tumors, and small-cell, we also do emphasize TNM staging, but I think what's probably more pertinent or relevant to clinical practices is the distinction between limited stage and extensive stage. The definition of limited stage small cell lung cancer is a disease that can be confined within a single radiation port. And I think that definition has evolved over the years, especially with more advanced radiation techniques. But essentially, these are cases we'll wanna review in our tumor boards, with our radiation oncologist, to really determine whether a patient has disease that could be easily encompassed within a safe and tolerable radiation field. And even cases of patients who have maybe more distant nodal disease can be characterized as having limited stage. Unfortunately, most of our patients are going to be presenting with extensive stage disease and this is disease really outside of the lung. It's very frequent for our patients to have brain metastases, or liver or bone metastases, and of course, those patients fall into the extensive stage category. When we're thinking about limited stage small cell lung cancer patients, about a third of our patients with small cell will present with limited-stage disease, we will want to discuss the minimal multidisciplinary tumor board setting in order to establish whether these patients would be suitable candidates for definitive chemo/radiation.

Dr. Sands:
Now, in the extensive stage setting, immunotherapy has become part of the standard of care. And of course, immunotherapy has revolutionized so much within oncology. But certainly, first-line small cell lung cancer, what has been your experience in that setting and

can you speak a bit to the trials that have led to that new standard of care?

Dr. Das:
Of course. Immunotherapy has been the latest and greatest advance in cancer treatment in general. And, of course, we saw in lung cancer, we saw the advances specifically in non-small cell lung cancer with early approvals of immunotherapy in the relapse setting and more recently in the first-line, advance-line setting and so now, of course, that's part of standard of care for non-small cell lung cancer. And then just in the past few years, we now also have approvals for immunotherapy in small cell lung cancer as part of frontline treatment.

The immunotherapy approvals actually started with nivolumab and pembrolizumab being approved based on early phase data in small cell lung cancer in the relapse setting, in those patients who had progressed on prior platinum-etoposide therapy. There appeared to be efficacy of single agent nivolumab and pembrolizumab based on early phase data, which led to accelerated FDA approval of these agents. So those were our first immunotherapy approvals in small cell lung cancer.

More recently, we have data from the IMpower133 trial, which showed a survival benefit with the addition of atezolizumab to platinum-etoposide in the frontline setting in our patients with extensive stage small cell lung cancer. There was about a 2-month survival benefit seen with the addition of atezolizumab, leading the FDA to approve atezolizumab, as part of frontline therapy for our patients with extensive stage small cell, really changing our treatment paradigm. And then about a year later we got the FDA approval for durvalumab in combination with carboplatin-etoposide, and that was based on the phase 3 CASPIAN trial, again, showing about a 2-month survival benefit with the addition of the durvalumab to platinum-etoposide. Both atezolizumab and durvalumab are PDL1 antibodies and did show efficacy again in combination with platinum-etoposide. After up-front systemic therapy for four cycles, the PDL1 inhibitor was continued on as maintenance therapy and this is really now our standard of care for our patients with extensive stage small cell lung cancer, is to offer these patients platinum-etoposide in conjunction with a PDL1 inhibitor, either atezolizumab or durvalumab based upon the positive randomized phase 3 data.

Dr. Sands:
So, we did see the splash of a new approval in the second-line setting with lurbinectedin? And then more recently there was the negative randomized trial, which was a combination of lurbinectedin with doxorubicin. But I also hear many people still saying, "Hey, I've had good experiences with single agent," and so what do you make of the data for lurbinectedin and what's been your experience?

Dr. Das:
Yeah, certainly when lurbinectedin was approved in June of 2020, it really represented an exciting alternative treatment regimen for this disease, which is very difficult to treat where we have very limited treatment options. Traditionally, the only FDA approved option for relapse small cell lung cancer has been topotecan and so it was very nice to have the option now of lurbinectedin.

I hadn't really been using topotecan as much. I've been using a similar drug, irinotecan, in the relapse setting, but now with the approval of lurbinectedin, I've essentially switched over to using this in patients with relapse small cell lung cancer. The schedule is a bit more attractive than irinotecan; it's given IV every three weeks. Irinotecan when I was giving it was sort of on a weekly schedule: three weeks on, one week off. And in my experiences, this tends to be a fairly well-tolerated drug. There is significant neutropenia, associated with the drug, so I do tend to give growth factor support when I'm administering the drug.

In the phase 2 basket trial, lurbinectedin did show efficacy, particularly in those patients with platinum-resistant disease. And so we know, patients who've relapsed beyond 60 to 90 days from having received their last platinum dose are considered to be platinum-sensitive, and you can consider rechallenging these patients with platinum-etoposide. Many of our patients unfortunately develop platinum-resistance disease which is relapse within a 60-to-90-day period of having received their last platinum-dose. And for these patients, the treatment options are very limited.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands and I'm speaking with Dr. Millie Das about advances in small cell lung cancer.

Dr. Das, so, prophylactic cranial irradiation. This was an established standard of care previously, but has now become an area of further research and discussion. Can you talk a little bit about prophylactic cranial irradiation, and some of the data, and why there's now some debate about it? And also just your practice or your recommendation? Obviously, this is all in collaboration with radiation oncology, but give us your perspective on it.

Dr. Das:
I think the data that we have to date really supports the use of PCI, particularly in our patients with limited stage disease. But I think over the years, many of us have been somewhat reticent to use PCI, given the potential for longer term cognitive side effects related to this.

And so I have certainly been speaking to my radiation oncology colleagues very closely about whether or not it makes sense to have a patient undergo PCI. I think that the stage is certainly important. I think the data is more supportive of PCI in our patients with limited stage disease, which is really a minority of our patients. For extensive stage disease, there's been a lot of recent controversy about the efficacy of PCI. There've been trials that have actually compared patients with extensive stage disease receiving PCI versus close brain surveillance and really failed to show a survival benefit in those patients receiving PCI. Which has really steered me away from recommending PCI to our patients with extensive stage disease, who are otherwise able to undergo close brain surveillance. And so that's really my preference in our patients with extensive stage disease.

For limited stage patients, I will have a discussion about the PCI and refer these patients to meet with a radiation oncologist. I will, however, mention that many of our patients with small cell are elderly, they have comorbidities, and I think there's a lot of risks and benefits that need to be discussed with the patient. It may or may not make sense to pursue PCI based upon the potential for side effects. You know, we do have some more recent advances in radiation technique including hippocampal sparing and the administration of memantine to try to reduce some of those cognitive side effects. And so again, I think it's important to discuss with the patient their preferences, to let them know the data, to let them know why we may be recommending for or against PCI in their particular case and to have it really be a joint decision between the patient, the medical oncologist, and the radiation oncologist to really determine what the best path forward would be. But in general, I tend to recommend it more strongly for my limited stage patients and really opt for the close brain surveillance in our extensive stage patients.

Dr. Sands:
So in the second- and third-line setting, aside from lurbinectedin, which we've discussed, there are various other treatment options, of course. You touched on irinotecan and topotecan as the other FDA approved option, which I know you said is not something that you're as enthusiastic about using. I think that's true of a lot of oncologists that treat small cell. But what are some of the other options that you're utilizing? And maybe you can also touch on, you know, pembro and nivo were previously approved in the third-line setting and now with some negative trials, those applications have been pulled, it sounds like. But, are those something that you still consider in those settings? What does the other landscape look like for you in that?

Dr. Das:
Especially in light of the more recent approvals for atezolizumab and durvalumab as part of frontline therapy, I think the relevance of using nivolumab or pembrolizumab in the relapse setting has really gone down because most of the times, when these patients have progressive disease, they're already received immunotherapy. And with the recent FDA withdrawals of nivolumab and pembrolizumab, again, I don't see that it's as clinically relevant, given that we're using atezolizumab and durvalumab as part of a frontline in maintenance therapy.

For patients again who have platinum resistant disease, I tend to go with either the lurbinectedin option or irinotecan, and I've been tending to prefer the lurbinectedin option just, again, given the schedule of IV every three weeks. Many of my patients live quite a distance and it's much more convenient for them to be able to just come in once every three weeks rather than on a weekly schedule.

For patients who have progressed on lurbinectedin or irinotecan, there are a number of other options that have shown efficacy in the relapse small cell lung cancer setting. Although, I'll be frank in that once patients are sort of in the third- or fourth-line setting, they're often times, very symptomatic from their disease. They're performance status may have declined. And you know I think it really takes a detailed discussion with the patients about the risks and benefits. Most of these drugs have significant side effects which really need to be considered when you're thinking about offering additional therapy in this setting. So, for a patient who has maintained adequate performance status who wants to be aggressive and wants to receive additional therapy, there are a number of other options. I've used single-agent taxane, I've also used Temodar, which is an oral chemotherapeutic option, which seems to show even more efficacy when used in combination with a PARP inhibitor, such as olaparib, though I think in my experience, it's been very difficult to get insurance to authorize this drug combination. CAV is a drug regimen that was used many years ago, and I've actually have had recent experience in using this three-drug combination. We don't really know that it's any better than any of our other single agent options, but for patients who have, again, maintained good functional status, want to be aggressive, have progressed on prior lines of therapy, there are a number of these other less-used options that can be considered.

Dr. Sands:
So looking forward, there's so much happening right now in small cell lung cancer. What are some of the things that you're excited about that maybe will be part of our standard of care discussion going forward, in the future?

Dr. Das:
I'm excited about the recent work that's looked at PARP inhibitors in patients with small cell lung cancer. I think there's a number of ongoing trials. Investigating PARP inhibitors, either in combination with chemotherapy or immunotherapy or some of our other novel

agents. And so I think there's been some recent work looking at SLFN11 being a potential marker, biomarker, of response to the PARP inhibitors. And so, traditionally we haven't really been able to figure out specific biomarkers in small cell lung cancer. But I think that that hopefully will be changing as we are seeing some of these potential biomarkers that can predict response to certain drugs. We know that PDL1 generally hasn't been a great biomarker of response to immunotherapy so there is a lot of work looking at other potential biomarkers of response to immunotherapy, so those patients who are going to be those exquisite responders to immunotherapy who really represent the tail of those curves that we saw in the CASPIAN and IMpower133 trials, really trying to identify those patients up front. I'm hoping that we'll continue to make progress in trying to identify what is it about that patient that's going to predict them responding well to immunotherapy.

Dr. Sands:
Well, there is so much to discuss in small cell lung cancer, but that does bring us to the end of today's program. I want to thank my guest, Dr. Millie Das, for joining me to discuss advances in small cell lung cancer. Dr. Das, absolute pleasure having you on the program today.

Dr. Das:
Likewise. Thanks so much, Jacob.

Dr. Sands:
I'm Dr. Jacob Sands. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology, where you can be part of the knowledge. Thanks for listening.