New Therapy Options in Small Cell Lung Cancer (SCLC) Webinar Transcript

Dr Amit Jain

Introduction – Dr Amit Jain

***Dr Tanujaa*:** Dr Amit Jain is a senior consultant medical oncologist at National Cancer Centre Singapore he's just completed his PhD and his research interest is in the field of cancer immunology and he is currently exploring the use of cell therapies for cancer.

Paradigms in Treatment of Extensive SCLC

Dr Jain: I would like to just go through a few paradigms in the treatment of extensive small cell lung cancer that we face as medical oncologists in the clinic. The standard of care is based on clinical demonstration of efficacy rather than a mechanistic understanding of the disease. Most of the first line therapies that we use work in a majority of patients but unfortunately the development of resistance is almost universal. This is a cancer which appears to have a lack of actionable biomarkers even though lots of RB and p53 proteins are common, these are actually rather difficult to target. Enthusiasm for ongoing development of clinical strategies is moderated by historical failure in improving the lethality of this disease.

SCLC – A Challenging Disease

Dr Jain: In Singapore approximately 10 to 15% of lung cancers are small cell lung cancer accounting for about 150 to 200 new cases a year. This is a cancer that is largely a man-made epidemic, it can be attributed to smoking related carcinogens. The cancer is an aggressive cancer with a short doubling time of 25 to 30 days, and this means that without treatment typically patients may only survive weeks. With treatment survival is still dismal, overall survival at five years is generally quoted to be less than 7%. The lethality of this cancer unfortunately has not changed in the last four decades despite this being one of the most extensively tested cancers in both the preclinical and clinical settings.

Amongst newly diagnosed SCLC, 60 to 70% of patients are diagnosed with extensive this stage disease that is incurable. As I mentioned earlier, this disease has not been able to be genomically and immune categorized in terms of lending clinical insights into sub-populations that have different susceptibility. Nevertheless, we continue to be enthusiastic with what may come in the future and currently more than 270 active or recruiting clinical trials are listed on clinicaltrials.gov. This represents a rapid trial and error approach to applying allegiance to this disease that continues to be an unmet need or agents that can traverse the brain, and this is particularly important because amongst all the small cell lung cancer patients we see up to

10% of them may present with brain metastases and unfortunately up to 40% them may experience brain metastases in their lifetime.

Chemotherapy in 1st and 2nd Line

Dr Jain: I am going to quickly summarize chemotherapy use in the first- and second-line setting. Four to six cycles of platinum doublet therapy is well established in the first line. Generally, one would choose carboplatin if there's any issues with whether patients can tolerate cisplatin. The platinum agent of choice may be combined with the etoposide or irinotecan depending on which part of the world one practices in.

Majority of patients unfortunately will still experience relapse within the first year of treatment. There are several labels that may be clinically useful if relapse occurs during treatment, we might call this platinum refractory disease and if it happens within 90 days of completing treatment, we call it platinum resistant disease and if it happens after 90 days then we call this platinum sensitive disease. This is relevant for patients who might be eligible for re-challenge with first line in the setting of platinum sensitivity where rechallenge is preferable. In the second line setting, topotecan remains the only formally approved treatment option and this was derived from a clinical trial comparing topotecan against best supportive care which gave a median overall survival of 26 months in the topotecan arm as compared to 14 months in the arm with best supportive care. Nevertheless, the response rates are modest at best between 10 to 20%.

There are multiple agents that have been tested in the first- and second-line setting, and these have been done in earlier phase clinical trials and therefore are included in the NCCN compendium of active agents that can be used against this disease.

Use of Immunotherapy in 1st Line

Dr Jain: Briefly, the use of immune checkpoint inhibition in the first line has been defined now by the use of atezolizumab and durvalumab in combination with platinum doublet therapy as the speakers before me have mentioned. It is important though to understand that this is in the context with other trials that have not given a clear signal of activity and at least one trial (IDEATE Phase 3) that has read out negative for the addition of immune checkpoint inhibition. Beyond the use of immune checkpoint inhibitors along with platinum doublets, atezolizumab and durvalumab also can be used as maintenance.

Use of Immunotherapy as Maintenance and in 2nd Line

Dr Jain: And this is currently the state of the art for the use of immunotherapy as maintenance in the second line setting. There are some negative trials (Checkmate-451, PIII; Checkmate-331 PIII, Multiples Phase I/II) again that are worth highlighting however in the context of several earlier phase trials that have shown some benefits in the second line setting onwards several immune checkpoints are also included in the NCCN guidelines.

NCCN Guidelines

Dr Jain: As per NCCN guidelines you can see that the first line treatment is defined by a platinum doublet therapy. This can be a platinum drug either in the form of carboplatin or cisplatin combined with either etoposide or irinotecan and given along with immune checkpoint inhibitor which can be either atezolizumab or durvalumab. In the 2nd line setting onwards there are now two preferred regiments either use of topotecan or now lurbinectedin. There are also multiple other agents that have been tested in early phase trials and in phase II setting largely which can be used both as IV and oral agents as well as immune checkpoint inhibitors pembrolizumab and nivolumab.

Lurbinectedin – Key Points

Dr Jain: A few key points to highlights and what we currently understand about how lurbinectedin may play a role in a patient's life. This drug is now approved for use as a single agent based on a Phase II study that showed an overall response rate of 35% amongst 105 patients with a median duration of response of about 5 months. Cytopenia has been the main side effect, and this was given in the setting of patients who had received platinum-based chemotherapy in the first line setting.

In a phase 3 clinical trial called ATLANTIS, lurbinectedin was combined with doxorubicin and compared against CAV or CA + topotecan, while it missed its primary endpoint, it demonstrated tolerability and overall activity in patients. One previous speaker has talked about the combination of Irinotecan and lurbinectedin and this combination will progress into advanced stage clinical trials, and it appears to be promising thus far.

Three early phase ongoing trials that combine immunotherapy with lurbinectedin will be informative for how we can combine checkpoint inhibition with lurbinectedin in the patients who have received first line treatment.

Treatments on the Horizon

Dr Jain: Beyond these drugs that we have mentioned there are other treatments that are in the horizon and there are some challenges with some of what has already been tested. While I mentioned earlier the loss of p53, RB1 proteins and the amplification of *myc* is very common in SCLC and these pathways continue to be extremely challenging to target.

There are multiple novel agents that include PARP inhibitors (Veliparib), alkylating agents (Temozolomide), VEGF inhibitors (Pazopanib) and Aurora kinase inhibitors (Alisertib) that are currently being tested in both phase I and phase II setting. A brief mention is worthwhile for the first targeted therapy that was developed for SCLC which is DLL3 that initially appeared to be a promising target for SCLC and the drug Rovalpituzumab-tesirine is an antibody drug conjugate that was tested with promising results in the Phase I study however in Phase II study with low rates of response and due to toxicity, it appears that the product has now been withdrawn from further testing.

So, looking to the future what we hope additional clinical trials will give us insights into are the optimal sequencing of platinum doublet, immunotherapy, lurbinectedin, single agent chemotherapy and how we can combine these drugs best. And to do that in the context of patients with varying degrees of platinum sensitivity in order to improve the life spans of our patients with extensive stage SCLC.

Case Study

Dr Jain: I'll briefly go through a case study. Here I describe one of my patients in clinic, a 66-year-old gentleman was diagnosed with extensive stage SCLC in July 2018 with the liver metastasis and was treated with good response with six cycles of platinum doublet therapy. In view of his good response, we considered him for consolidation radiation to the thorax as we hoped it would improve his outcomes. After discussion at a multidisciplinary tumor board, we made the decision to proceed with consolidation radiation and he received 36 Grays in 12 fractions in February 2019. Subsequently and unfortunately, he developed pneumonitis which appeared to have elements of both interstitial pneumonitis as some of the areas that were involved appeared to be outside of the radiation field and there certainly seemed to be an element of radiation pneumonitis as well. We treated this with steroids as well as steroid sparing agents and in consultation with the respiratory doctors. The patient had good disease control for 18 months and had some control over his pneumonitis but thereafter there was a slow progression of his disease. In view of his poor function as well as his preference for an oral form of treatment, I offered him temozolomide. He had an initial partial response that subsequently progressed within two months. Thereafter, the patient was offered best supportive care with home hospice support, and he deteriorated gradually passing away in May 2021.

With the current set of approvals that are now available for small cell lung cancer, there are an increasing number of options that might be available. And for patients like this, where one might be extremely nervous to give any form of immune checkpoint inhibitor, they may be suitable for single agent therapy or new agents such as lurbinectedin.