The Role of Immunotherapy in Small Cell Lung Carcinoma

Executive Summary

Small cell lung carcinoma is an aggressive cancer that originates from neuroendocrine cells, mostly in the lungs. Lung cancer is the most common form of cancer related deaths, claiming an estimated 1.59 million deaths globally per year. In the US, lung cancer was responsible for 234,000 deaths in 2018, and an estimated 154,000 new cases will be diagnosed this year *(Siegel et al, 2018).* Small cell lung cancer (SCLC) accounts for 15% of all lung cancer cases and in approximately 90% of cases is due to smoking. SCLC is characterized by an aggressive course and early metastasis, high tumor heterogeneity and a poor prognosis.

SCLC tumors are highly proliferative, and show good response to CT and radiotherapy, but almost all patients will relapse within few months. Approximately 70% patients present with metastatic disease that has spread outside the hemithorax, classified as extensive stage SCLC (ES-SCLC) and have a poor prognosis, with a median survival of 8 to 10 months when treated with standard CT. The 5-year survival rates from the time of diagnosis is 2%.

The outcome is slightly better in stage I or limited stage(LS)-SCLC with a median overall survival (OS) of 23 months and a 5-year survival of around 30% when treated with CT and radiation (*Roche Media Release, 2018; BMS Press Release, 2018)*. There has been limited progress in the treatment of SCLC in the past two decades with treatment limited to conventional CT and radiation, creating a desperate need for novel targeted therapies in this aggressive disease.

There has been limited progress in the treatment of SCLC in the past two decades with treatment limited to conventional CT and radiation, creating a desperate need for novel targeted therapies in this aggressive disease. The discovery of inhibitory pathways that can negatively regulate immune response directed against tumor cells has led to the development of targeted agents for treatment. Immunotherapy is an exciting area of research in small cell lung cancer and holds the promise to extend survival and improve outcomes.

Moreover, the FDA has recently approved immune checkpoint inhibitor nivolumab in monotherapy in patients with pretreated ES-SCLC, and the drug was previously approved alone or in combination with ipilimumab in second line therapy. Numerous clinical trials are now investigating immune check point inhibitors alone or in combination with CT and radiation, and are advancing to later stages with encouraging results.

In the face of rapid developments, oncologists and allied health practitioners must be educated about the latest advances in the management of SCLC, the rationale for immunotherapy and the immune related adverse events, and the latest safety and efficacy trial data. Ongoing education and training of the scientific community will surely improve survival and patient related outcomes for SCLC patients

Gap 2 : Physicians may not be knowledgeable about the standards of care and guideline recommendations of SCLC.

There is wide variability in the application of oncology guidelines, and many barriers prevent their implementation. A lack of time to review the guidelines, the lack of specificity of patient factors that can sufficiently guide treatment may be the reasons for this gap. Targeted educational activities at providers

caring for cancer patients, increased visibility of the published clinical pathways, and implementation of feedback programs were shown to improve physician adherence to guidelines and subsequently the quality of care *(Kubal et al, 2016, Hermann et al, 2015)*. Moreover, Shikdar and colleagues showed a suboptimal level of compliance to lung cancer guidelines by oncologist physicians, that warranted action *(Shikdar et al, 2018)*

The standard of care for ES-SCLC consists of CT with 4 cycles of etoposide/platinum with a response rate of 80%. Despite a high response to initial CT, tumors are highly resistant once progression has occurred. Most patients will progress during first line treatment and the disease will relapse. There are few options for second line treatments after relapse, topotecan is the only FDA approved and offers a median OS of 6-7.8 months, with a 1 year survival of 10-30%. Amrubicin is approved in Japan, with comparable OS and higher ORR with better hematological profile *(Majem and Rudin, 2017a)*

There is no standard of care in subsequent lines of therapy, and no targeted therapy has been identified to date, in the treatment of SCLC.

Intracranial metastases occur in 50% of patient with SCLC. Patients with limited stage SCLC, with good initial response, prophylactic cranial irradiation (PCI) decreased brain metastases and improve OS *(NCCN, 2018a*). In ES-SCLC that has responded to systemic therapy, patient with a good PS and stable disease (SD), PCI decreases the emergence of brain metastases *(NCCN, 2018a; Slotman et al, 2007; Slotman et al, 2015)*. Thoracic radiation may be considered in low bulk metastatic ES-SCLC that has responded to CT, and may improve survival after systemic therapy *(NCCN, 2018a).*

The National Comprehensive Cancer Network (**NCCN)** guidelines for SCLC recommend platinum based CT with a regimen of cisplatin or carboplatin in combination with etoposide

In extensive stage disease, recommendations is to treat with a maximum of 4-6 cycles of either:

- Carboplatin or cisplatin in combination with etoposide
- Carboplatin or cisplatin in combination with irinotecan

In second line therapy, NCCN guidelines refer patients to clinical trials. In cases of relapse within 6 months, in good performance status, several agents may be tried. They are recommended by the NCCN in the following order of preference as topotecan, irinotecan, paclitaxel, docetaxel, temozolomide, nivolumab+/-ipilimumab, vinorelbine, oral etoposide, gemcitabine, cyclophosphamide/doxorubicin/vincristine (CAV) (all category 2A); and bendamustine (category 2B).

However, these have failed to yield substantial advantages over traditional CT. If relapse occurs longer than 6 months, patients may be re-challenged with original treatment. None of the second line therapies significantly prolong survival but they are palliative in nature, and studies comparing CAV to topotecan or standard cisplatin etoposide failed to show any advantage *(NCCN, 2018a).*