Poly(Adenosine Diphosphate–Ribose) Polymerase Inhibition as Maintenance Treatment for SCLC: The Search Must Continue

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Extensive-stage SCLC (ES-SCLC) is an aggressive cancer and despite a high overall response rate (ORR) to first-line platinum-based chemotherapy, responses are unfortunately short-lived and the 5-year overall survival (OS) rate for ES-SCLC remains less than 5%.[1] Current first-line treatment regimens consist of platinum-based chemotherapy plus atezolizumab or durvalumab when indicated. Patients with platinum-sensitive disease (treatment-free interval $\geq$3 mo) are usually rechallenged with platinum-based chemotherapy. Patients with platinum-refractory or resistant disease may receive second-line chemotherapy with topotecan, VAC (vincristine, Adriamycin [doxorubicin], and cyclophosphamide), or lurbinectedin.[2] Unfortunately, second-line chemotherapies have limited efficacy, with ORRs of 7% to 24% and OS ranging from 3.2 to 8.7 months.[3–5] The poor outcomes from second-line chemotherapies and the lack of durable responses have led to a search for effective maintenance treatments. Two large meta-analyses evaluating different strategies have reported a small benefit in OS with high heterogeneity among the included trials.[6,7] It is important to point out that most of the randomized controlled trials did not reveal any significant OS benefit. For this reason, maintenance therapy has not been recommended after the completion of four to six cycles of chemotherapy.

More recently, the addition of programmed death-ligand 1 (PD-L1) inhibitors such as atezolizumab[8] or durvalumab[9] to platinum-etoposide chemotherapy followed by maintenance PD-L1 inhibition has exhibited longer OS when compared with chemotherapy alone. These first-line regimens changed the practice for selected patients with ES-SCLC and have now supported the role of maintenance immunotherapy. Not all patients with SCLC will be a candidate for immune checkpoint blockade, and therefore, the research on maintenance strategies must continue.

In this issue of the Journal of Thoracic Oncology, Ai et al.[10] reports the findings of the randomized phase 3 trial ZL-2306-005, evaluating the safety and efficacy of niraparib as maintenance treatment for platinum-sensitive ES-SCLC. The dual primary end points were progression-free survival (PFS) and OS, and the trial was terminated early owing to the changing treatment landscape and the emerging use of immunotherapy in this setting. As a result, the analysis was performed with 185 out of the planned 591 patients. With the limitation of this underpowered analysis, there was no improvement in terms of PFS or OS for niraparib over placebo. The OS analysis suggested that, at the interim time point analysis, niraparib had a lower OS than placebo; however, robust conclusions regarding the efficacy should not be drawn.

Recent years have led to advances in the understanding of the pathogenesis of SCLC and potential targets for treatment. Most of the mutations found in SCLC are somatic mutations induced by the carcinogens found in smoking.[11] The biology of SCLC is mostly driven by TP53 and Rb1, and these are notably difficult molecular targets. Platinum chemotherapies crosslink with purine bases in DNA and cause DNA damage, which triggers apoptosis. Poly(adenosine diphosphate–ribose) polymerase (PARP) is a group of enzymes that detect single-stranded DNA breaks, leading to DNA repair.[12] By inhibiting the DNA repair process, the apoptotic process is initiated. Niraparib is an inhibitor of the PARP 1 and 2 enzymes licensed for the maintenance treatment of a variety of

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platinum-sensitive gynecologic cancers.[13] However, SCLC has not been proven to express mutations in DNA repair genes such as BRCA 1 or BRCA2, and these are not predictive of response to PARP inhibition.[14]

Rudin et al.[15] reported the heterogeneity of the transcriptomics and cellular structures of SCLC by describing the changing expression of oncogenes during the progression of SCLC in human xenograft models. Simpson et al.[16] reviewed mouse and human models of expression of transcription regulators and proposed key subtypes of SCLC defined by differing expressions of defined transcription factors. The SCLC-A subtype was defined by the expression of the ASCL-1 transcription factor, which plays a key role in pulmonary tissue neuroendocrine differentiation.[17] The SCLC-A subtype may respond to a combination of PARP inhibition and PD-L1 blockade.

Researchers from MD Anderson Cancer Center confirmed the four SCLC subtypes with differing expressions of transcription factors ASCL1, NEUROD1, and POU2F3 or low expression of all three transcription factors accompanied by a defined gene signature (SCLC-A, N, P, and I, respectively).[18] These groups were initially identified applying nonnegative matrix factorization to previously published data from 81 patients with SCLC with surgically resected tumors. To validate the four subtypes, they also analyzed data from 276 patients with SCLC enrolled in the IMpower133 clinical trial. This study found that each subtype had different tendencies to respond to checkpoint inhibition or inhibitors of PARP, Aurora kinases, or BCL-2. Interestingly, SCLC-A xenografts treated with cisplatin shifted the gene signature to SCLC-I, suggesting a mechanism of acquired platinum resistance.

SLFN11 is implicated in regulating DNA damage responses and replicative stress[19] and it may be a predictive marker of response to DNA-damaging chemotherapy regimens and PARP inhibitors.[20,21] A randomized phase 2 trial investigating temozolozide in combination with veliparib or placebo in relapsed platinum-sensitive or refractory SCLC found no difference in PFS or OS.[22] Exploratory objectives included PARP-1 and SLFN11 immunohistochemical expression, MGMT promoter methylation, and circulating tumor cell quantification. Patients with SLFN11-positive tumors treated with temozolomide/veliparib had a longer PFS (5.7 versus 3.6 mo; $p = 0.009$) and OS (12.2 versus 7.5 mo; $p = 0.014$), indicating that this could be a potential predictive biomarker for this strategy. An early phase trial evaluating temozolomide and olaparib in previously-treated SCLC reported an ORR of 41.7%.[23] There was a correlation between low basal expression of inflammatory response genes in patient-derived xenografts and cross-resistance to both temozolomide and first-line platinum-based doublet chemotherapy.

An ongoing phase 2 trial (NCT04334941)[24] is randomizing patients with SLFN11-positive ES-SCLC to receive atezolizumab or atezolizumab plus talazoparib as maintenance therapy. KEYLYNK-013 (NCT04624204)[25] is a phase 3 trial, which randomizes patients with limited-stage SCLC to receive concurrent chemo-radiotherapy with or without pembrolizumab followed by maintenance pembrolizumab with or without olaparib. Notably, patients enrolled in this trial will not be selected on the basis of any biomarker.

Recent preclinical and translational data suggest that PARP inhibitors may have a role in the treatment of SCLC, in particular, as maintenance therapies. Results of ongoing studies will shed more light on the efficacy of this strategy and it is hoped that it will help to identify potential predictive biomarkers for appropriate patient selection.

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