Review Article

Immune checkpoint inhibitors and small cell lung cancer: what's new?

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Abstract: Despite extensive research no meaningful progress in systemic treatment of small cell lung cancer (SCLC) has been made in the past decades. Earlier attempts with immunotherapy including interferon and vaccination approaches had limited success. High mutational load, smoking history and potentially also the frequent presence of paraneoplastic phenomena—indicating an activated immune system—represent a rationale for a benefit from immune checkpoint inhibitors in SCLC. However, the likelihood of response is diminished due to poor T-cell activation resulting from low expression of MHC class I antigens, low amounts of tumor infiltrating lymphocytes (TILs) and low PD-L1 expression rates. Recently, early reports from studies with checkpoint inhibitors have shown promising results with the potential for long term disease control in a subset of SCLC patients. However, reliable predictive biomarkers to better define the population drawing most benefit are currently lacking. Results from ongoing phase III trials in different treatment lines and in the maintenance setting are eagerly awaited.

Keywords: Small cell lung cancer (SCLC); checkpoint inhibitors; predictive biomarkers

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Introduction

Lung cancer is the leading cause of cancer related mortality and an estimated 1.8 million new lung cancers are diagnosed worldwide each year. The proportion of small cell lung cancer (SCLC) is estimated around 13%, with a history of tobacco use in literally all patients (1). Approximately 70% of the SCLC patients present with stage IV disease, where the treatment approach is palliative. Standard treatment in Western Countries in these patients is combination chemotherapy with either cisplatin or carboplatin and etoposide (2,3). Although this regimen achieves high response rates (RR) of 65–70%, outcomes are poor with a median overall survival (OS) of <10 months due to early drug resistance and rapid tumour progression (4). Despite extensive research no meaningful progress has been made with systemic treatment in the past decades. Repeated efforts of integrating immunotherapy into SCLC treatment have been made with only little success in the past years. These approaches included interferons, which enhance major histocompatibility complex (MHC) class I expression, but neither for the combination of low-dose interferon with chemotherapy in the first-line setting (5) nor for maintenance treatment with interferon alone or in combination with retinoid acid after induction chemotherapy or chemoradiotherapy have eventually demonstrated any significant benefit (6,7). The same is true for vaccinations: ganglioside antigen (GD3) is overexpressed in SCLC in approx. 60% of cases (8). Therefore, Bec2 anti-idiotypic antibody that mimics GD3 seemed a promising target, but a large phase III trial with the antiganglioside vaccine Bec2/Bacille Calmette-Guerin (Bec2/BCG)

vaccination in the adjuvant setting after Chemotherapy and chest radiotherapy in limited stage SCLC did not show improved outcomes (9).

Early results from studies with immunotherapy checkpoint inhibitors now finally show some promising outcomes in a subset of patients with the potential for improvement of survival in a field where it is much needed (8,10-12). We will focus our review on immune checkpoint inhibitors in patients with SCLC.

Perspectives of immunotherapy in SCLC

Mutational burden has been proposed as predictive biomarker for checkpoint inhibitor treatment in several tumour types including NSCLC (13). In line with previous studies comprehensive genomic profiling of 110 SCLC specimens showed very high mutation rates (14-16). Tumor-suppressor-genes *TP53* and *RB1* were altered in all but two cases supporting hypothesis that complete genomic loss of both *TP53* and *RB1* function is obligatory in the pathogenesis of SCLC, leading to increased genomic instability. In addition the carcinogenic effect of tobacco is associated with a higher mutational burden (10). In other tumour entities such as NSCLC, smoking-related lung cancers are characterized by a greater mutation burden compared to never smokers (17) and response to immunotherapy has consistently shown to be better in patients with a smoking history compared to never smokers in large phase III trials (18-20). Overall high mutational burden and the almost universal smoking history of SCLC patients would favour improved outcomes of immunotherapy in these patients.

Autoimmunological paraneoplastic syndromes including neurological and endocrinological phenomena are quite common in SCLC patients, suggesting an activated immune system in these patients. In a series of 170 SCLC patients presence of anti-Hu antibodies was an independent factor for complete response to therapy in a multivariate analysis and as opposed to the majority of SCLC patients, MHC class I proteins were not down-regulated if anti-Hu antibodies were present, potentially rendering these patients more sensitive to immune response (12,21,22). On the other hand, potential enhancement of response may also imply higher risk for neurological autoimmune phenomena as encephalitis and myasthenia gravis (23). Therefore, toxicity needs to be closely monitored, as in other tumour entities that are typically accompanied with paraneoplastic phenomena such as thymomas where serious autoimmune related side effects have been observed (24).

Tumour-infiltrating lymphocytes (TILs) in the tumour as potential predictive biomarker for checkpoint inhibition are less common in SCLC and are mostly found at the tumour periphery at the border of tumour and stroma and not within the tumour (25,26).

One reason for the relatively marginal T-cell recruitment in SCLC could be the reduced or absent MCH class I expression on SCLC tumor cells. Tumor antigens are presented to the immune system by MHC class I surface antigens. Reduced or absent MHC class I expression leads to decreased antigen presentation to cytotoxic T-cells (CTLs) (25). In SCLC cell lines and fresh tumor samples reduced expression of MHC class I surface antigens could be shown despite intact MHC class I genes, indicating a block in mRNA transcription (27), unlike it is the case in NSCLC cell lines. Interferons are known to augment MHC class I in melanoma cells (28) and Doyle *et al.* could show, that interferons also can increase HLA expression in SCLC cell lines, where these have been markedly decreased (27). Balance of T effector cells (Teff) and T regulatory cells (Treg) seems to play an important role in SCLC as Teff/Treg-ratio corresponds with risk of recurrence in an analysis of 35 patients with SCLC with long-term survivors maintaining a high ratio of Teff to Treg cells and patients with recurrent disease a low ratio, respectively (29). Also, high number of lymphocytes in the peripheral blood correlated with better survival (30). In summary low expression of MCH class I antigens leads to decreased T-cell recruitment, explaining low numbers of TILs within the tumor in SCLC patients, being a negative predictive marker for response to immunotherapy.

Programmed death-ligand 1 (PD-L1) expression status of tumor cells is used to identify patients who might be more likely to benefit from immune checkpoint inhibitors. However, PD-L1 status is influenced by various factors such as intratumoral heterogeneity, dynamic changes over time and the availability of various different test methods using different thresholds for PD-L1 positivity (31,32). In SCLC, data on PD-L1 expression are controversial but overall expression seems to be quite low. In the recent checkmate-032 trial only 18% of patients had a PD-L1 expression >1% and expression status was not relevant for response to treatment and outcomes (23). In an analysis of 94 small cell specimens (61 of the lung, rest extrapulmonal) analyzed for PD-L1 expression on tumor cells and microenvironment none of the analysed tumor cells stained positive for PD-L1, whereas in 18.5% of cases

PD-L1 positive cells (mainly monocytes) in the adjacent stroma were found. In 48% of cases PD-1 positive TILs were found, although not also TILs were seen mainly at the border of tumor and stroma, not within the tumor (26). This is supported also by a study by Rivalland *et al.* presented at ASCO 2017, where in 105 SCLC specimens analysed tumor cells positive for PD-L1 expression were only found in a minority of cases (18%) (33). On the other hand, other studies demonstrated high PD-L1 expression in SCLC specimens (34-36).

In conclusion, although high mutational load and presence of paraneoplastic phenomena represent a rationale for potential benefit of immunotherapy in SCLC patients, latter may harbour the risk of increased autoimmunological side effects. In addition, T-cell activation is poor due to low expression of MHC class I antigens and TILs are uncommon in the vast majority of SCLC specimens as is the relatively low rate of PD-L1 expression lowering the likelihood of response to immune checkpoint inhibitors.

Clinical trials with immune checkpoint inhibitors in SCLC

First line treatment

First promising signs of activity of checkpoint inhibitors as novel immunotherapeutic approach came from a phase II trial of the CTL4-antibody ipilimumab in combination with carboplatin and taxol first-line in extensive stage SCLC with improved progression-free survival (PFS) compared to chemotherapy alone when given in a "phased" fashion meaning the introduction of immunotherapy after 2 cycles of chemotherapy (37). However, the following phase III trial was negative regarding its primary endpoint overall survival (OS) for the combination of platinum/etoposide in combination with ipilimumab which was again administered as phased treatment in the same patient population (38). Nevertheless, a similar approach is now being investigated targeting the PD-1/PD-L1 axis amongst others in three large trials: KEYNOTE-604 comparing pembrolizumab plus etoposide/platinum to chemotherapy alone (NCT03066778), IMpower133 which compares atezolizumab with carboplatin and etoposide to chemotherapy alone (NCT02763579) and CASPIAN studying durvalumab alone or in combination with tremelimumab with platinum based chemotherapy followed by durvalumab ± tremelimumab maintenance therapy versus chemotherapy alone (NCT03043872), all in the first-line setting.

Maintenance treatment

Initial high tumor burden and the often-rapid response with chemotherapy in the 1L-setting followed by early drug resistance and rapid tumour progression theoretically favour the investigation of maintenance treatment regimens to delay progression and improve overall survival. At ASCO 2017 a phase II study of maintenance pembrolizumab in 45 patients with extensive stage small cell lung cancer was presented, however no improvement in PFS could be demonstrated (39). Checkmate-451, a randomized placebo-controlled phase III trial investigating a similar approach with nivolumab alone or in combination with ipilimumab finished recruiting (NCT02538666). The phase II IMPULSE trial investigating maintenance treatment with the TLR9 agonist Lefitolimod has finished recruiting, results are awaited NCT02200081.

Second or later line treatment

For treatments targeting the PD-1/PD-L1 axis first reports for activity came from multi-cohort studies including SCLC cohorts: Keynote-028, a phase 1b multi-cohort trial with pembrolizumab as well as Checkmate-032, a phase I/II trial with nivolumab alone or the combination of nivolumab and ipilimumab.

Results from the SCLC cohort of Keynote-028, which only included PD-L1 positive (>1%) patients, were first reported at the WCLC 2016 by Ott *et al.* and recently published (40). Twenty-four SCLC patients with extensive disease and at least one prior treatment line were treated with pembrolizumab 10 mg/kg every 2 weeks. In this cohort confirmed overall response rate (ORR) was 33% with one complete remission (CR) and median duration of response was 19.4 months. OS was promising in this heavily pre-treated patient population with 9.7 months with a 12-month OS rate of almost 40%. However, although promising survival data were observed in second line also including poor prognostic platinum resistant patients, this trial was very small and the subset of likely highly selected responders consisted of eight patients only, of whom five received treatment for over 1 year. Results of lager trials have to be awaited in order to draw definitive conclusions about the activity of single agent pembrolizumab in this situation. Trials with pembrolizumab with the current standard dose of 200 mg every 3 weeks are ongoing in PD-L1 unselected patients (KEYNOTE 158) as well as in the first-line and maintenance setting and in combination with

chemotherapy or chemoradiotherapy (NCT03066778, NCT02359019, NCT02934503).

Another small phase Ia trial investigated the anti-PL-L1 monoclonal antibody atezolizumab as a monotherapy in 17 heavily pre-treated SCLC patients. The trial showed a confirmed ORR by RECIST in only 1 patient (6%) (41).

Checkmate-032 was a larger phase I/II trial that enrolled a total of 216 patients who were unselected for PD-L1 status and progressing after at least one previous platinum-containing regimen into three different SCLC cohorts (23). Patients were treated either with nivolumab 3 mg/kg every 2 weeks alone or in combination with ipilimumab in a safety dose-escalating manner with the dose of nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks followed by nivolumab 3 mg/kg every 2 weeks emerging as the regimen for succeeding studies due to favourable PFS of 2.6 months which was numerically higher than in the other cohorts (1.4 and 1.4 months). ORR was 25% in the combination-arm but only 11% in the nivolumab monotherapy arm with a median duration of response of 11.7 months. Median OS was markedly shorter than in the keynote 028 trial with 4.4 months for monotherapy and 7.9 months for the combination. However, the 2-year OS rate of 26% suggests that a subset of SCLC patients may derive long-term benefit. Outcomes in this trial were independent of PD-L1 expression, which was only positive in a minority of patients (18% >1% PD-L1 expression) and unrelated to platinum-sensitivity. Interestingly, similarly to NSCLC (13) high tumor mutational burden (TMB) measured by whole exome sequencing emerged as possible predictive biomarker in an exploratory analysis presented at WCLC 2017 (42). TMB was classified into three groups based on number of nonsynonymous somatic mutations: high (>243 mutations), medium (100–243 mutations) and low (<100 mutations). ORR to combination treatment was 46% in the TMB high group versus 16% and 22% in the intermediate and low groups. This was reflected also by a markedly higher 1-year PFS rate of 30% in the TMB high group receiving combination treatment versus 8 and 6% in the intermediate and low groups. The same tendencies were also shown for patients receiving monotherapy but ORR was lower than in the combination arms in all patients. Although these results are derived from a relatively small exploratory subgroup analysis (n=26), particularly 1-year PFS rate in the TMB high group appear very promising and potentially identifies a proportion of patients who may have prolonged disease control in this poor prognostic group of patients. Overall, combination treatment seems more effective, but treatment toxicity has to been taken into account, particularly with the SCLC population outside of clinical trials who are often older and frail due to tobacco-associated comorbidities. In the combination arm with nivolumab 1 mg/kg and ipilimumab 3 mg/kg (n=61) the rate of adverse events (AE) was 79% and grade 3–4 adverse events (AEs) occurred in as many as 30% of patients. Seven patients (11%) discontinued treatment because of toxicity and two patients died due to treatment-related AEs. Importantly, neurological autoimmune events occurred in three patients having limbic encephalitis, including one patient with grade 4 not resolving despite i.v. corticosteroids and immunoglobulins, and one patient dying with myasthenia gravis, indicating that these side effects may be observed more frequently in these patients than in other malignancies.

A number of trials in the second-line setting are ongoing with a focus on combination therapies such as the phase 1/2 trial investigating Rovalpituzumab Tesirine [a delta-like 3 (DLL3) directed anti-body drug conjugate] with nivolumab or in combination with both nivolumab and ipilimumab (NCT03026166) and the first in class Fucosyl-GM1 mAb, a fully human mAb with enhanced antibody-dependent cell-mediated cytotoxicity that binds to fucosyl-GM1, a ganglioside highly expressed on SCLC, in combination with nivolumab (NCT02247349).

Limited stage

Adjuvant treatment with ipilimumab and nivolumab after completion of curative chemoradiotherapy in limited stage SCLC is being evaluated in the ongoing ETOP STIMULI trial (NCT02046733), results are awaited 2020.

Conclusions

After decades without relevant progress in treatment of metastatic SCLC, early trial results indicate that immunotherapy with checkpoint inhibitors may have the potential for long-term disease control in a subset of patients. Results from currently ongoing large phase III trials in first and later lines as well as in the maintenance setting are eagerly awaited. Combination immunotherapy appears to be more active than single agent anti-PD-1/PD-L1 therapy, although more toxic. Therefore, it will be particularly important to identify predictive markers in order to better select patients drawing benefit from treatment. Early results are indicating that high TMB

may be of interest for selection of anti-PD-1/CTLA-4 combination. In this regard, further analyses of ongoing clinical trial are eagerly awaited.

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Footnote

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