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Immunotherapy treatments for small-cell lung cancer: past, present and future

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Summary

Small-cell lung cancer remains a considerable cause of morbidity and mortality. To this day, first-line therapy continues to be a platinum agent with etoposide, combined with radiation therapy in cases of limited stage disease. Numerous, largely unsuccessful, attempts at controlling the disease have included different chemotherapy strategies, the utilization of antiangiogenic agents, tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors and other treatment modalities. Immunotherapy, including vaccines, immune response modifiers, inhibitors of check point blockades and immunologic-targeted toxins may well be the future of treatment, not only to enhance the proven chemotherapy effects, but to improve the control of minimal residual disease and the response with salvage chemotherapy. This article reviews the current advances in immunotherapeutic strategies against small-cell lung cancer.

Lung cancer remains the leading cause of cancer-related mortality for both men and women in the USA [101]. The Surveillance Epidemiology and End Results database estimates that 228,190 people in the USA will be diagnosed with cancer of the lung and bronchus in 2013 [101]. Small-cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers and is notorious for its rapid doubling time, propensity for metastases and high growth fraction. While SCLC is commonly responsive to both chemotherapy and radiotherapy initially, the response is rarely durable, with disease relapse, characterized by chemotherapy resistance, typically occurring within several months. First-line therapy has long been recognized as a platinum agent with etoposide for 4–6 cycles [1]. If the disease happens to encompass one radiation port, it is termed limited stage and concurrent radiation therapy is given. The addition of early radiation therapy to the platinum and etoposide increases 2-year survival by 5–7% in limited stage disease [2,3]. Although limited stage and extensive stage disease respond to appropriate first-line therapy 70–90 and 50–70% of the time,

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respectively, relapse is common and 5-year survival is 10–25% for limited stage and 1–2% for extensive stage [4].

The treatment regimens and associated outcomes described above have been in place for over three decades and their limitations have triggered the testing of a number of strategies in an attempt to improve the current disease outcomes. Among them are: alternating, noncross-resistant chemotherapy regimens [5]; the addition of a third cytotoxic agent [5]; dose escalation and dose dense regimens [6,7]; the use of growth factor support [8]; maintenance [9] and consolidation [10] chemotherapy; and high-dose chemotherapy [11]. All of these strategies have only rendered disappointing outcomes either because of inferior or negative results or because of excessive toxicities that made the strategy impractical.

With improvements in our understanding of molecular biology, more modern strategies have also been applied. Unfortunately, so far they have been equally unsuccessful.

Antiangiogenic agents, such as bevacizumab and thalidomide, have been studied as adjuncts to first-line therapy in extensive stage disease without large success. The SALUTE study, a blinded randomized Phase II study, compared the addition of bevacizumab versus placebo to a platinum agent and etoposide [12]. This study reported in 2011 that the addition of bevacizumab prolonged the progression-free survival (PFS) from 4.4 to 5.5 months, but unfortunately overall survival (OS) showed no significant benefit [12]. A Phase III trial randomized both extensive stage and limited stage SCLC patients to receive either thalidomide or placebo in addition to carboplatin and etoposide [13]. There was no difference in median OS in limited stage disease and reduced OS in extensive stage disease [13]. mTOR inhibition with temsirolimus failed to show improvement in OS compared with historical controls when used as a maintenance agent [14]. The tyrosine kinase inhibitors imatinib, gefitinib and dasatinib were all studied in Phase II trials and failed to show improvements when used in the maintenance or relapsed setting [15–17]. Insulin-like growth factor 1 (IGF-1) receptor inhibitors, hedgehog inhibitors, Aurora A kinase inhibitors, poly ADP ribose polymerase (PARP) inhibitors and histone deacetylase (HDAC) inhibitors are all currently being investigated. A relative success of bendamustine in relapsed or refractory SCLC was seen in a Phase II study, with a 30% objective response rate [18]. The only approved agent for second-line therapy is single-agent topotecan, with a dismal response rate of 24.3% and median OS of 25 weeks [19]. Depending on the duration of response to the platinum and etoposide (first-line therapy), retreatment with the same can be entertained [20]. Needless to say, improved treatment options are overdue.

Recent advances have been made using immunotherapeutic agents in the treatment of melanoma, renal cell carcinoma, non-small-cell lung cancer (NSCLC) and other solid-tumor malignancies. Vaccines for NSCLC in particular are in the advanced stages of development [21]. In theory, SCLC lends itself well to immunologic control. It has long been associated with paraneoplastic processes such as inappropriate secretion of antidiuretic hormone (SIADH), cerebellar degeneration and limbic encephalitis mitigated by anti-Hu paraneoplastic antibodies, and Lambert–Eaton myasthenic syndrome, suggesting a link with the immune system [22,23]. In addition, minimal residual disease (MRD), which is often readily achieved by chemotherapy in SCLC, may be an optimal time to incorporate immunotherapy. In MRD, the disease burden is low, which allows higher tumor infiltration

by T-effector cells and has lower levels of myeloid-derived suppressor cells, which are known to suppress the immune system [24]. Furthermore, longer survival has been seen in SCLC when there is high tumor infiltration by CD4⁺, CD8⁺ and dendritic cells. Conversely, disease recurrence is correlated with high expression of regulatory T cells, which are immunosuppressive [25]. Patients with high blood T-effector cell to Treg ratios are more likely to have limited stage than extensive stage disease, thus adding to the evidence that immune surveillance is of critical importance [26]. There are multiple strategies to provoke a cancer-controlling immunologic response that have been investigated in recent years in SCLC, namely vaccines, immune response modifiers and immunologic-targeted toxins. Trials with the newer inhibitors of checkpoint blockade are also currently underway. This article reviews the current advances in immunotherapeutic strategies against SCLC.

Vaccines

The theorized idea of vaccines as a way to control MRD stems from the fact that tumor cells express a variety of antigens, or tumor-associated antigens, that are not normally found on physiologic cells [27]. In SCLC, the tumor cells are known to express a variety of antigens including GD1–3, GM1–3, polysialic acid, globo H, sialyl Le, KSA and bombesin [27]. Carbohydrate antigens in general are not effective immunogens, as they are largely T-cell independent and do not induce memory cells or significant antibody titers [28,29]. The GM3 ganglioside on the SCLC tumor cells, in particular, are not immunogenic given their glycolipid nature [29]. Thus, a major difficulty that must be overcome in the vaccine development field is the enhancement of the immune response to SCLC cells.

The monoclonal antibody (moAb) BEC2 is an antibody that is directed at R24, which is relatively specific for GD3. By using R24 as a target as opposed to GD3, the immune system is presented with an antigen that leads to a greater immune system response [27]. Using this theory, vaccination with the anti-idiotypic BEC2 and Bacillus Calmette–Guerin was tested and found to induce anti-GD3 antibodies in three of 14 patients with melanoma [30]. In 1999, results of a 15-patient study evaluating a similar immunization strategy (anti-idiotypic antibody BEC2 combined with Bacillus Calmette–Guerin) in SCLC showed that OS and PFS were improved compared with historical controls [31]. The BEC2 antibody is thought to mimic cell surface ganglioside GD3, which is expressed on most SCLC, while Bacillus Calmette–Guerin served as the immune adjuvant to stimulate antibody formation [31]. While all patients developed anti-BEC2 antibodies, five patients developed measurable anti-GD3 antibodies and had the longest PFS [31]. A Phase III study using this approach as adjuvant therapy in limited stage SCLC after chemoradiotherapy enrolled 515 patients and was reported in 2005 [32]. Although no improvements in OS, PFS or quality of life were seen, the study showed a trend toward improved OS in those patients that developed a humoral response (one third of the vaccination arm), suggesting that a vaccine producing a better immunologic response might still be valuable [32].

Another vaccine utilizing the anti-idiotypic 1E10 (1E10 anti-Id) moAb was developed in mice immunized with P3 mAb, which recognizes one of the previously mentioned GM3 gangliosides [29]. After animal models showed a promising antitumor effect with 1E10 anti-Id mAb, three Phase I studies in patients with breast cancer, melanoma and SCLC revealed

the development of anti-anti-Id Ab responses to the GM3 tumor-associated antigens [29]. In addition, the patients in the SCLC study had a prolonged survival compared with historical control (20–36 vs 10–18 months) [29,33]. This is an impressive result that has warranted an ongoing Phase III study comparing racotumomab, formerly called 1E10, to best supportive care in patients with NSCLC (NCT01460472). Krug *et al.* has recently reported on a Phase I study evaluating the safety and minimum immunogenic dose of *N*-propionylated-polysialic acid (polySA) conjugated to keyhole limpet hemocyanin vaccine [34]. At the 10 µg dose level, all of the patients responded with IgM antibody titers against polySA and all but one made both IgM and IgG antibodies against *N*-propionylated-polySA [34]. Further plans include the development of *N*-pro-pionylated-polySA into a polyvalent vaccine with target antigens of GD2, GD3, fucosylated GM1 and globo H, all known to be expressed on SCLC cells [34].

Personalized peptide vaccination, in which vaccine antigens are selected based on existing host immunity, have also been studied in a small Phase II study of ten patients with refractory SCLC. In the six patients that received the complete first cycle without rapidly progressing, the survival time of 6–25 months is encouraging and warrants further prospective trials [35].

Altered tumor suppressor p53 function, usually a result of point mutations or abnormalities in degradation of wild-type p53, is found in approximately 50% of all human cancers and >90% of SCLC [36]. The resulting mutated protein induces MHC class I expression of p53-derived epitopes on the malignant cell surface (tumor-associated antigens), making it a suitable target for immune recognition [37–39]. In 2006, Antonia *et al.* first reported on a Phase I/II study of patients with extensive stage SCLC, previously treated with chemotherapy, who were treated with a vaccine consisting of dendritic cells transduced with full-length wild-type *p53* gene delivered by an adenovirus [40]. Although no verified clinical responses were noted and all 29 patients except one had progressive disease, a p53-specific immune response was detected in approximately 57.1% of patients and, more interestingly, a high rate of objective clinical responses to subsequent (salvage) cytotoxic chemotherapy (61.9%) was noted [40].

The completed trial utilizing the manufactured p53-modified adenovirus-transduced dendritic cell vaccine, developed at the H Lee Moffitt Cancer Center, included 54 extensive stage SCLC patients who had been previously treated with chemotherapy. Of the 43 patients evaluable for immune response, 18 patients (41.8%) had a positive immune response (as determined by a p53-specific ELISPOT assay). The study then evaluated the relationship between immune response and salvage chemotherapy. A significant clinical response was seen in 11 of 14 (78.6%) patients who had a positive immune response compared with only five of 15 (33.3%) patients with a negative immune response. The median OS was 12.6 months in those with an immune response compared with 8.2 months in patients without ($p = 0.131$) [36].

Finally, a randomized study involving SRL 172, a suspension of killed *Mycobacterium vaccae*, was undertaken with chemotherapy in patients with SCLC [41]. Patients who were randomized to the vaccine arm were given an intradermal injection on weeks 0, 4, 8, 12 and

16 in addition to standard chemotherapy [41]. Unfortunately, after 55 events the study was closed due to poor accrual and little difference in the two arms. Although no significant differences in the overall response rate or OS were seen, the results suggest that symptomatic response was improved in the vaccine arm without any difference in toxicity [41].

Immune response modifiers

Providing a more fertile microenvironment suitable for immune response is associated with an improved response to immunotherapy [42]. This section focuses on factors that can putatively yield a greater immunologic response from immunotherapeutic vaccination.

Building on the results from the p53-modified adenovirus-transduced dendritic cell vaccine study previously described, the Moffitt Cancer Center (FL, USA) is completing a randomized Phase II study (NCT00617409) in a similar population of patients with SCLC, where in addition to a control (nonvaccine) group, a second group receives the vaccine in a similar fashion as before and a third group also receives all-trans-retinoic acid (ATRA) in an attempt to influence the action of myeloid-derived suppressor cells (MDSC) [102]. MDSC are pathologically activated immature polymorphonuclear and mononuclear cells that suppress immune activity [43]. Additional observations have correlated a high metastatic solid-tumor burden with high levels of MDSC [44]. Recently, a preliminary report of immunologic results of this randomized trial included 41 patients and determined that depletion of MDSC using ATRA improved the immune response to vaccination with the p53-transduced dendritic cell vaccine [43]. Similarly, in another study, higher probability of pathologic complete response was seen in patients with lower levels of MDSC [45].

With the background of preclinical data showing that indeolamine 2,3 dioxygenase is an inducible enzyme that some tumors use to down-regulate the immune system [46], the Moffitt Cancer Center reported at the American Society of Clinical Oncology 2013 Annual Meeting, on a Phase I study of the same p53-transduced dendritic cell vaccine in combination with indoximod in metastatic solid tumors [46]. Indoximod modulates the indeolamine 2,3 dioxygenase pathway and the observation that it enhances the immunologic response to vaccines is leading to a planned Phase II trial in metastatic breast cancer evaluating indoximod and ad.p53 dendritic vaccine followed by salvage chemotherapy (NCT01042535) [46].

Cytokines such as IFN and IL-2 are of critical importance in the development of a proper microenvironment for immune system function. IFN binds to cell receptor sites and stimulates production of proteins and regulatory factors that promote anticancer effects. Many of these effects are mitigated through tumor vascular endothelial proliferation, endothelial migration or antiangiogenic proteins [47,48]. IFN- α has been studied as an adjunct to cytotoxic chemotherapy beginning in the 1980s. In SCLC, maintenance low-dose IFN- α compared with maintenance chemotherapy or observation alone in previously treated patients was evaluated in a Phase III trial in 1992. While there was no difference in median OS, a survival improvement in the limited stage population that received IFN- α maintenance was noted [49]. A second Phase III trial, where IFN- α was combined with induction

chemotherapy, failed to increase the OS, and more concerning, a reduction in the 2-year survival rate was suggested by increasing grade 3 and 4 leukopenia necessitating suboptimal chemotherapy doses [48,50]. Toxicity concerns, without survival advantage, have also been raised in patients with SCLC receiving radiotherapy concurrently with IFN- α [51]. IFN- α maintenance, with or without retinoic acid, has also been compared in a feasibility study to a group receiving no maintenance therapy after combination chemotherapy. They too found no statistical difference in the duration of response or time to progression [52]. Zarogoulidis *et al.* recently conducted a Phase II trial evaluating the addition of IFN- α , IFN- γ or IFN- α plus IFN- γ to chemotherapy alone in treatment-naïve patients [53]. They found no statistical difference in OS or response rates when all patients were considered, but found an OS benefit for the group receiving IFN- α with chemotherapy who had limited stage disease [53].

Tumors can also evade the immune system by causing a decrease in the production of endogenous IL-2, altering the signal cascade of these cytokines, or an increase in the production of immunosuppressive cytokines to counteract stimulatory effects [54–56]. Low-dose IL-2 and 13-*cis* retinoic acid was evaluated in a Phase II pilot study in 2002 in 80 patients with advanced solid tumors after standard chemotherapy [57]. The results indicated that there was a significant increase in the number of total lymphocytes, T4/T8 ratio and NK with the therapy in 7.5%, with only grade 2 cutaneous toxicity and fever in 29 and 13% of patients, respectively [57]. A recent abstract presented at the American Society of Clinical Oncology 2013 Annual Meeting looked to confirm the pilot study results. In this Phase II study, patients with high-risk solid tumors whom had response to chemotherapy received low dose IL-2 (1.8 million units subcutaneous Monday through Friday, 3 weeks on and 1 week off), oral isotretinoin 0.5 mg/kg on the days of IL-2 and/or subcutaneous peg-IFN 50 μ g weekly. From the total of 68 patients who were evaluable (including NSCLC), there was one progression, 26 had stable disease, three were in partial remission and 38 maintained or achieved complete responses [58]. While these studies did not appear to include SCLC patients, the findings suggest potential future applicability of this strategy in the disease.

Inhibitors of checkpoint blockades

Immune checkpoint blockades are a well-described mechanism that allows attenuation of the antitumor effect of T cells. The best known checkpoint blockade is cytotoxic T-lymphocyte antigen-4 (CTLA-4). This is a potent negative regulator of T-cell activation, which is used by many tumors to evade immune surveillance [59]. Ipilimumab is a fully humanized anti-CTLA-4 mAb that blocks the binding of CTLA-4 with its ligands, CD80 and CD86, resulting in continued activation of the T cells [60,61]. The success of ipilimumab has been shown in two large randomized studies of patients with metastatic melanoma where a significant prolongation of OS was described [62,63].

In SCLC, a blinded Phase II trial was conducted evaluating ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in extensive stage patients [64]. A total of 130 treatment-naïve patients were randomized to receive paclitaxel, carboplatin and either placebo, concurrent ipilimumab (ipilimumab plus chemotherapy starting with the first cycle) or phased ipilimumab (ipilimumab plus chemotherapy starting with the third cycle) [64].

Maintenance placebo or ipilimumab continued every 12 weeks thereafter [64]. Although no PFS improvement was detected by traditional methods, phased ipilimumab resulted in improved immune-related PFS, with a hazard ratio of 0.64 [64]. Immune-related PFS is a novel concept developed to document the unique tumor responses observed with ipilimumab, including a reduction in size of index lesions in the face of new lesions and tumor enlargement followed by stabilization or regression [64]. Furthermore, a trend toward improved OS of 12.9 versus 9.9 months suggests that the timing of immunologic intervention with respect to chemotherapy is important and that further investigation of the phased ipilimumab arm is warranted [64].

An ongoing, randomized Phase III trial is aiming to determine whether a phased schedule of ipilimumab combined with carboplatin and etoposide extends overall survival as compared with patients treated with carboplatin and etoposide alone (NCT01450761) [103]. Another clinical trial currently enrolling patients aims to evaluate a PFS improvement with the addition of ipilimumab to carboplatin and etoposide at 1 year [104].

The programmed death 1 (PD-1) receptor is expressed on activated T cells, B cells, NK cells, activated monocytes and activated dendritic cells and, when binding to PD-1 ligands on stromal and tumor cells, results in the downregulation of the immune system cell [25,65,66]. In the normal host, it serves as an important regulator of the immune system, protecting the body tissues from unopposed activation of the T cells. Similar to CTLA-4, inhibition of the PD-1 receptor with a moAb results in the inability of tumor PD-1 ligands to bind to this receptor, causing continued activation of the T cell; inhibition of this pathway has potent antitumor effects [67–69]. While no studies have been published using PD-1 or PD-L1 antibodies in SCLC, numerous studies are documenting their success in treating NSCLC, melanoma, renal cell carcinoma and other advanced cancer [21,62,67,70,71].

The concurrent use of anti-CTLA-4 and anti-PD-1 moAbs in a preclinical murine adenocarcinoma model was recently presented at the 2013 American Society of Clinical Oncology Annual Meeting [72]. The dual inhibition resulted in a synergistic antitumor effect, postulated as a result of increased expression of intratumoral cytokines rather than increased T-cell infiltration [72]. This preclinical model helped spur dose escalation trials of combined nivolumab, a PD-1 inhibitor, and ipilimumab (NCT01928394).

Immunologically targeted toxins & oncolytic viruses

Recent approval of trastuzumab emtansine, an Ab–drug conjugate linking the moAb trastuzumab to the cytotoxic agent mertansine, for metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer has enlightened the medical field to Ab–drug conjugates. In 2007, McCann *et al.* reported on a Phase II trial of HuN901-DM1, a humanized antibody–maytansinoid immunoconjugate that binds to CD56, in patients with relapsed SCLC or other small-cell carcinomas [73]. CD56 is expressed in the vast majority of cases of SCLC and other small-cell carcinomas, neuroendocrine carcinomas and multiple myeloma [73]. In particular, 19 out of 19 SCLC tissue samples were positive for CD56 in a 2002 study and 98.9% of 88 SCLC tissue samples expressed CD56 in a recent 2013 study [74,75]. The study reported that, out of 30 patients treated, one patient with SCLC had an

objective partial response lasting 18 weeks and five patients had stable disease lasting between 6 and 18 weeks [73]. Four patients has serious drug-related adverse events, consisting of severe headache in three patients who markedly improved after 24 h and one patient with grade 4 hyperesthesia [73]. The study concluded that the immunoconjugate appeared safe when using premedication with steroids to prevent headaches [73].

Anticancer viruses have not taken a firm hold in the treatment of cancer due to, among other things, problems with generating high viral titers, preexisting immunity in much of the population and the lack of selective tropism for cancer cells [76,77]. However, the Seneca Valley Virus (SVV-001), an oncolytic virus, was studied in a Phase I trial of SCLC patients. They documented good tolerance, evidence of intratumoral viral replication and evidence of antitumor activity [76]. A Phase II study is currently ongoing (NCT01017601).

Future perspective

Given the well-known limitations from current treatment options against SCLC patients, advances in immunotherapy open the field to future immunologic strategies that are ripe for development. Many preclinical and early phase studies have shown strong evidence that incorporation of immunologic agents such as vaccines, checkpoint inhibitors and targeted toxins to traditional therapy can yield substantial results, with manageable toxicity. Furthermore, because chemotherapy and radiation induce significant responses in most of these patients, more investigation is required in areas such as MRD. Additional investigation of combinations of immunotherapy plus chemotherapy may also render a prolongation in the tumor time to progression and in the efficacy of subsequent therapy, including chemotherapy. These trials are currently underway and clearly indicate that immunologic adjuncts to standard SCLC therapy may very well be the future for this difficult disease.

The advances of immunotherapy as treatment for SCLC have uncovered several challenges that warrant further investigation. These challenges include finding the optimal timing and/or schedule of immunotherapy, its use in combinations with chemotherapy, the delayed time in immune responses sometimes seen, and the lack of appropriate immune-competent animal models and effective biomarkers capable of selecting subgroups of responders.

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Practice points

- The treatment of small cell lung cancer (SCLC) has not significantly changed in over three decades and remains a chemotherapy combination, with the addition of radiotherapy for patients with limited stage disease.
- Minimal residual disease achieved in SCLC after initial (chemo-/radio-)therapy may be an opportune scenario where immunotherapy may prove valuable.
- Considerable progress has been made in vaccine development for SCLC, although none are yet available outside of a clinical trial.
- Encouraging a fertile microenvironment for immunotherapy is important. IFN, IL-2, indoximod and suppression of myeloid-derived suppressor cells with retinoic acid may achieve this goal.
- Inhibitors of checkpoint blockades such as ipilimumab, anti-programmed death (PD)-1 and anti-PD-L1 have shown considerable success in other solid tumors, and are exciting. Phased ipilimumab in combination with chemotherapy showed an immune-related progression-free survival improvement and a trend toward improved overall survival in SCLC. Trials with anti-PD-1 or anti-PD-L1, specifically in SCLC, are in development.
- Immunologically targeted toxins and oncolytic viruses are still in their infancy, but have promise in the treatment of SCLC.
- The absence of predictive models of response to immunotherapy strategies remains a challenge that needs to be resolved.