Review Article

A narrative review of salvage therapy in small cell lung cancer

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Contributions: (I) Conception and design: SV Liu; (II) Administrative support: SV Liu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Small cell lung cancer (SCLC) is an aggressive subtype of lung cancer, responsible for a disproportionate number of lung cancer deaths. Most patients present with advanced disease, where systemic therapy is the primary treatment. While SCLC is initially sensitive to cytotoxic chemotherapy, responses are transient and upon relapse, SCLC is relatively refractory to therapy. The addition of immunotherapy to front-line treatment for SCLC has improved survival, but most patients will still have relapse of their disease and at that time, options are limited. Retreatment with platinum based chemotherapy remains a viable option for patients who have had a longer chemotherapy free interval. Topotecan and lurbinectedin are both cytotoxic agents that are approved in the second line setting as monotherapy. While both agents are active, outcomes remain somewhat modest and are balanced by toxicity. Amrubicin is an agent approved in some parts of the world, but randomized studies failed to demonstrate improvement over standard topotecan. Other cytotoxic agents have been studied that offer comparable efficacy, though data sets are limited. Immunotherapy, specifically nivolumab and pembrolizumab monotherapy, is an approved option as third-line monotherapy but the impact has been lessened with the integration of checkpoint inhibitors in the first-line setting. An understanding of which other agents have activity in this setting is increasingly relevant for the management of relapsed SCLC.

Keywords: Small cell lung cancer (SCLC); immunotherapy; chemotherapy; salvage

Received: 23 March 2020. Accepted: 27 August 2020; Published: 30 September 2020.

doi: 10.21037/pcm-20-24

View this article at: http://dx.doi.org/10.21037/pcm-20-24

Introduction

Small cell lung cancer (SCLC) is a relatively uncommon but exceptionally lethal neuroendocrine subtype of lung cancer. Most patients are diagnosed at an advanced stage where the current standard is chemo-immunotherapy (1-4). Unfortunately, the vast majority of patients relapse within the first year and progression free survival (PFS) is typically limited to less than 6 months (5,6). Even for the minority of patients with early (limited-stage) SCLC, relapse is expected. Upon relapse, only two agents are currently approved in the US as second-line therapy and in general, response rates (RR) are low and PFS is short (7). Given the high relapse rate, understanding the efficacy of the limited therapeutic options for this aggressive cancer remains ever relevant. This narrative review provides a summary of the current landscape of salvage therapy for SCLC.

Methods

A systematic literature search was conducted using PubMed for manuscripts that discussed salvage therapy for SCLC. Prospective trials were included as were original retrospective reviews. Abstracts from 2017–2020 from global meetings were also included, specifically the annual meetings for the American Society of Clinical Oncology

(ASCO), the American Association for Cancer Research (AACR), and the International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC). We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/pcm-20-24).

Chemotherapy

Cytotoxic chemotherapy has been the mainstay of treatment for extensive-stage (ES) SCLC for decades. The platinum-etoposide (EP) chemotherapy backbone showed initial efficacy in the 1970s and remained the standard until the recent addition of atezolizumab improved OS (8,9). With EP alone, responses are frequent (RR 61%) and can be deep [complete response (CR) rate 10%], but the benefit remains transient (median PFS 4.3 months) and survival is limited (OS 8.6 months) (6). Upon relapse, there are several active cytotoxic regimens currently in use.

Retreatment with platinum/etoposide

Under certain clinical circumstances, revisiting platinum-based chemotherapy is an appealing option. For patients with previously treated SCLC who received salvage teniposide, the RR was 42% in patients who had responded to prior chemotherapy but 0% in patients (0/7) who did not respond to prior chemotherapy (10). For patients who last received chemotherapy more than 2.6 months before teniposide, the RR was a robust 53%, versus only 12% in patients who last received chemotherapy within 2.6 months. Based on these data, when patients relapse long after completing chemotherapy, retreatment with that same regimen may be an active option (11). Traditionally, patients who initially respond then relapse more than 60–90 days after the completion of chemotherapy are classified as having a 'sensitive relapse', and those who relapse within 60–90 days as 'refractory relapse.' (12). However, terminology (which may include sensitive, resistant, and refractory) varies considerably between studies (13-15).

A multi-center retrospective study evaluated platinum and etoposide re-challenge in 112 patients with platinum-sensitive SCLC (16). For this study, platinum-sensitive relapse was defined as a relapse-free interval (RFI) of 90 days or more. When re-challenged with EP, outcomes were favorable with a CR rate of 3%, a partial response rate (PR) of 42% and stable disease in an additional 19% of patients. The median PFS was 5.5 months and the median OS was 7.9 months. The OS from time of diagnosis was 21.3 months, though 44% of patients had LS disease at the time of diagnosis. Longer RFI (beyond 90 days) did not confer further improvement in outcomes; patients with an RFI of 90, 120, or 150 days all had comparable median PFS (3.1 *vs.* 4.8 *vs.* 6.0 months) and median OS (8.2 *vs.* 11.9 *vs.* 7.9 months).

Another single-center retrospective study evaluated 300 patients with relapsed SCLC to assess responses based on platinum-sensitivity (17). Sensitive-relapse (n=143) was defined as an RFI of 90 days or more, resistant (n=72) as an RFI less than 90 days, and refractory (n=64) as no response to initial therapy. The overall RR to initial chemotherapy was 73%. The RR to second-line chemotherapy was 38% but varied by sensitivity; RR was 56% in the sensitive, 18% in resistant, and 14% in refractory patients. The OS was 23 months in sensitive, 10 months in resistant, and 6.4 months in refractory relapses. RR after third and fourth line of treatment was 24% in the sensitive group, 9% in resistant group, and no responses were observed in the refractory group.

The impact of platinum-sensitivity on response was also assessed in a 161-patient multi-center study of patients with relapsed SCLC after treatment with platinum plus etoposide (18). Platinum sensitive relapse (n=121) was defined as relapse after an RFI of at least 90 days, resistant relapse (n=29) as an RFI less than 90 days, and patients who progressed during initial therapy were considered refractory (n=3). Different regimens included platinum-based re-challenge (18%), vincristine plus doxorubicin and cyclophosphamide (VAC) or vincristine plus epirubicin and cyclophosphamide (45%), topotecan (22%), and monotherapy with taxanes, ifosfamide, vinorelbine or gemcitabine (15%). RR to second-line chemotherapy was 22.9% and was associated with response to first-line therapy (P=0.04). Patients retreated with platinum-based chemotherapy independent of platinum sensitivity, showed a reduction in mortality of 54% (HR: 0.46, 95% CI, 0.228–0.929; P=0.03), compared to other regimens. Multivariate analysis showed that performance status (HR: 1.91, 95% CI, 1.225–2.988; P=0.004) and response to first-line therapy (HR: 0.39, 95% CI, 0.174–0.872; P=0.022) were prognostic factors for survival.

In carefully selected patients with SCLC who have a platinum-sensitive relapse, re-challenging with platinum-based chemotherapy is a potentially effective option. For those in whom retreatment is not appropriate, the current standards of care in the US are topotecan and lurbinectedin.

Topotecan

Topotecan is a topoisomerase I inhibitor and is currently the only FDA-approved, second-line agent for patients with recurrent SCLC. A multi-center study that established topotecan as the standard of care randomized 211 patients with ES-SCLC to receive topotecan [administered at 1.5 mg/m^2 intravenously (IV) per day for 5 consecutive days, every 21 days] versus CAV (cyclophosphamide at 1,000 mg/m^2, doxorubicin at 45 mg/m^2, and vincristine at 2 mg, all administered every 21 days) (15). Efficacy between the two arms was comparable. The RR was 24% with topotecan and 18% with CAV (P=0.28); duration of response was 14 weeks with topotecan versus 15 weeks with CAV (P=0.3). Median time to progression was also similar at 13 weeks versus 12 weeks (P=0.05), respectively, and there was no difference in survival between the two arms: 25 weeks with topotecan and 24.7 weeks with CAV (P=0.79). There were some differences in toxicity. Adverse events overall were primarily hematologic; Grade 3–4 thrombocytopenia was more common with topotecan (10%) versus CAV (1%) and Grade 3–4 anemia was reported in 18% of patients with topotecan and 7% with CAV. Grade 4 neutropenia was higher in the CAV arm at 51% versus 38%. Importantly, more patients randomized to topotecan achieved an improvement in symptoms including dyspnea, fatigue and anorexia as compared to CAV, establishing topotecan as the preferred second-line option.

Subsequent trials confirmed the activity of topotecan (*Table 1*). A phase III randomized trial compared best supportive care (BSC) alone to BSC plus topotecan (IV) in 141 patients with relapsed SCLC (21). Topotecan was administered at 2.3 mg/m^2 per day IV, on days 1–5 of each 21 day-cycle. Topotecan improved OS (14 *vs.* 26 weeks; P=0.01) and improved quality of life. Notable toxicities from topotecan included grade 4 neutropenia (33%), grade 4 thrombocytopenia (7%), and grade 3/4 anemia (25%).

A randomized phase II trial was conducted to assess the efficacy of oral topotecan compared to standard IV topotecan (19). A total of 106 patients with relapsed SCLC were randomized to receive topotecan, either oral (2.3 mg/m^2/day) or IV (1.5 mg/m^2/day). Each treatment was given for 5 consecutive days in 21-day cycles. The RR and the duration of response were 23% and 18 weeks with oral topotecan, versus 15% and 14 weeks with IV topotecan. Reduction in symptoms including chest pain, shortness of breath, cough, and hemoptysis was comparable in the two treatment arms. Survival was not significantly different, with a median of 32 weeks in the oral group and 25 weeks in the IV group. Grade 4 neutropenia was lower with oral topotecan (35.3%) compared to IV topotecan (67.3%). Fever and infection occurred in 5.1% of patients receiving oral versus 3.3% with IV topotecan. Grade 3+ thrombocytopenia and anemia were also frequently seen, with comparable incidence in both groups.

These findings were confirmed in a phase III trial that randomized 309 patients to oral (n=153) or IV topotecan (n=151) (13). Efficacy was similar with the two formulations. The RR was 18% with oral topotecan and 22% with IV topotecan. The median time to response was 6.1 weeks in both groups, and the median duration of response was 18 weeks with oral topotecan and 25 weeks with IV topotecan. Median time to progression was also similar with oral and IV topotecan (12 and 14.6 weeks, respectively). The OS was comparable at 33 weeks with oral versus 35 weeks with IV group. One-year and two-year survival rates were 32.6% and 12.4% with oral topotecan and 29.2% and 7.1% with IV topotecan. The most common toxicity with both regimens was neutropenia, seen in 47% in the oral group compared to 64% in the IV group. Overall, these randomized studies demonstrated similar RR and OS with comparable safety profiles. Oral topotecan is a reasonable option for patients with relapsed SCLC.

An alternate dosing regimen was explored in a phase II trial using weekly IV topotecan at 4 mg/m^2/week for 12 weeks in 12 patients with relapsed SCLC (23). Compared to historic controls, relatively lower rates of grade 3–4 thrombocytopenia (17%), neutropenia (8%) and anemia (8%) were observed. Another schedule with IV topotecan given at 4 mg/m^2 on days 1, 8, and 15, every 4 weeks was studied in 22 patients with platinum-sensitive relapsed SCLC (20). None of the patients responded to the weekly regimen (RR 0%). Median PFS was 6 weeks and median OS was 5 months. Grade 3+ adverse events included thrombocytopenia (9%), dyspnea (9%) and fatigue (5%). Another phase II trial studied a higher dose of weekly IV topotecan (6 mg/m^2/week for 6 out of 8 weeks) in 38 patients with relapsed SCLC and reported a RR of 8%, stable disease in 24% and a median OS of 19.4 weeks (22). Major grade 3–4 toxicities included neutropenia (53%), leukopenia (42%), thrombocytopenia (37%), and anemia (13%). While toxicity with topotecan appears to be more modest with a weekly approach, efficacy also appears inferior across different (small) trials.

Outcomes with topotecan do vary between platinum-sensitive and platinum-refractory SCLC. A meta-analysis

Table 1 Select topotecan trials in relapsed SCLC

Author	Year	Patients (n)	Treatment	Overall RR (%)	Median PFS (weeks)	Median OS (weeks)	Grade 3+ Toxicities (%)		
							Neutropenia	Thrombocytopenia	Anemia
von Pawel *et al.* (15)	1999	211	IV topotecan	24	13	25	38	10	18
			CAV	18	12	24	51	1	7
von Pawel *et al.* (19)	2001	106	Oral topotecan	23	18	32	57	53	31
			IV topotecan	15	14	25	94	49	30
Shah *et al.* (20)	2007	22	Weekly IV topotecan	0	6	20	0	9	0
O'Brien *et al.* (21)	2006	141	BSC	NR	NR	14	NR	NR	NR
			Oral topotecan plus BSC	7	16	26	33	7	25
Eckardt *et al.* (13)	2007	309	Oral topotecan	13	12	33	47	29	23
			IV topotecan	22	14	35	64	18	31
Spigel *et al.* (22)	2011	38	Weekly IV topotecan	8	10	Sensitive: 34; Refractory: 14	53	37	13

BSC, best supportive care; CAV, cyclophosphamide plus doxorubicin plus vincristine; IV, intravenous; NR, not reported; OS, overall survival, PFS, progression free survival; RR, response rate.

of 14 trials analyzed outcomes with topotecan in relapsed SCLC by platinum-sensitivity, defining a sensitive relapse as one with an RFI of 60–90 days (24). With sensitive relapse, the RR was 17%, six-month OS rate was 57%, and 1-year OS rate was 27%. In the refractory relapse setting, the RR was 5%, six-month OS rate was 37%, 1-year OS rate was 9%. Adverse effects were mainly hematologic including grade 3–4 neutropenia (69%), grade 3–4 thrombocytopenia (41%), and grade 3–4 anemia (24%). Topotecan was the only FDA approved second-line agent for decades until the approval of lurbinectedin in 2020.

Lurbinectedin

Lurbinectedin is a promising new cytotoxic agent that inhibits the active transcription of protein-coding genes by causing DNA-break accumulation. It may also play a key role in modulation of the tumor microenvironment (25). In preclinical studies, lurbinectedin reduced the number of tumor-associated macrophages by inducing caspase-8-dependent apoptosis and inhibiting the production of inflammatory factors. A phase I study of lurbinectedin in patients with solid tumors established a safe dose of 4 mg/m^2 or 7 mg flat dose given IV, every 21 days (26). A separate phase I trial tested the combination of lurbinectedin (4 mg flat dose every 3 weeks) and doxorubicin (50 mg/m^2) in 27 patients with relapsed SCLC (27). In the 12 patients with platinum-sensitive relapsed SCLC (RFI ≥90 days), the RR was a striking 92% and median PFS was 5.8 months. There was also activity in the 15 patients with platinum-resistant SCLC (RFI <90 days), with a RR of 33% and a median PFS of 3.5 months. Notable grade 3–4 toxicities included neutropenia (95%), leukopenia (79%), anemia (47%), and thrombocytopenia (26%). Non-hematological toxicity included mucositis (11%) and fatigue (11%).

Another phase II trial investigated lurbinectedin (3.2 mg/m^2 every 3 weeks) monotherapy in 105 patients with SCLC who had received one prior line of chemotherapy/immunotherapy (28). The RR was 35.2%, median duration of response was 5.3 months, and median OS was 9.3 months. Outcomes varied by platinum-sensitivity. In the 60 patients with platinum sensitive relapse, defined as a chemotherapy-free interval of at least 90 days, the RR was 45% with a median duration of response of 6.2 months. PFS in those with sensitive relapse was 4.6 months with a median OS of 11.9 months and a 1-year survival rate of 48.3%. The study included 45 patients with a chemotherapy-free interval of <90 days, where activity was still noted. The RR in this group was 22.2% with a 4.7-month median duration of response. The PFS for this challenging subgroup was 2.6 months with a median OS of 5 months and a 1-year survival rate of 15.9%. Based on these promising data,

lurbinectedin received accelerated approval by the FDA as second-line therapy for patients with advanced SCLC.

Amrubicin

Amrubicin, a third-generation anthracycline and potent topoisomerase II inhibitor, was studied extensively in relapsed SCLC patients in multiple phase II clinical trials and has shown clear clinical activity (29-32). A phase II trial studied amrubicin 45 mg/m^2/day (administered on days 1–3, every 3 weeks, for four to six cycles) in 33 patients with refractory or relapsed SCLC (33). The RR was 53%, OS was 8.8 months, and the 1-year survival rate was 26%. The study showed high rates of severe hematologic toxicities including grade 3–4 neutropenia (97%), leukopenia (76%), and thrombocytopenia (38%). Another phase II trial studied amrubicin 40 mg/m^2 given for 3 consecutive days, every 3 weeks in patients with sensitive (n=36) and refractory-relapsed (n=16) SCLC (29). Sensitive relapse was defined as relapse with an RFI ≥ 60 days, and refractory as that with an RFI <60 days. The RR and PFS were 52% and 4.2 months in the sensitive group, and 50% and 2.6 months in the refractory group. OS was similar at 11.6 months in sensitive and 10.3 months in refractory patients, with corresponding 1-year OS rates of 46% and 40%. High rates of hematological toxicities including neutropenia (83%), thrombocytopenia (20%), and anemia (33%) were reported.

Given the encouraging results, a randomized phase II trial compared second-line amrubicin to topotecan in 60 patients with relapsed SCLC (sensitive = 36, refractory = 23) (30). In this study, sensitive-relapse was relapse with an RFI ≥ 90 days, refractory-relapse included patients with no response those with an RFI <90 days. Patients were randomized 1:1 to amrubicin (40 mg/m^2 on days 1–3) or topotecan (1 mg/m^2 on days 1–5). The RR with amrubicin was 38% and 13% with topotecan. The RR in sensitive-relapse was 53% with amrubicin *vs.* 21% with topotecan. The RR in refractory-relapse was 17% with amrubicin and 0% with topotecan. Median PFS was 3.5 months with amrubicin and 2.2 months with topotecan. Hematological toxicities were more frequent with amrubicin including grade 4 neutropenia (79% *vs.* 43%) and febrile neutropenia (14% *vs.* 3%). Higher grade non-hematologic toxicities were also greater with amrubicin. Another randomized phase II trial comparing amrubicin (n=50) to topotecan (n=26) in patients with sensitive-relapsed SCLC showed a higher RR of 44% with amrubicin versus 15% with topotecan (P=0.021) (32). The median PFS and median OS were 4.5 and 9.2 months with amrubicin, and 3.3 months and 7.6 months with topotecan. In contrast to previous studies, myelosuppression was greater with topotecan than amrubicin including Grade 3–4 neutropenia (78% *vs.* 61%) and grade 3–4 thrombocytopenia (61% *vs.* 39%).

Unfortunately, a phase III trial failed to show a survival benefit with amrubicin over standard topotecan (34). A total of 637 patients with platinum-sensitive (n=225) or refractory (n=199) SCLC were randomized 2:1 to amrubicin (40 mg/m^2 on days 1–3) or topotecan (1.5 mg/m^2 on days 1–5), both in 21-day cycles. Response was more likely with amrubicin (31% *vs.* 17%, P<0.001) but amrubicin failed to improve survival over topotecan. The median OS was 7.5 months with amrubicin and 7.8 months with topotecan, for a hazard ratio (HR) for death of 0.880 (95% CI, 0.733–1.057; P=0.170). In the subset of patients with platinum-refractory SCLC, outcomes did favor amrubicin. Response rate was higher with amrubicin than topotecan in the platinum-refractory subset (20% *vs.* 9.4%) and PFS was longer with amrubicin (4.1 *vs.* 3.5 months). However, survival was similar in patients with platinum-refractory SCLC; median OS was 6.2 with amrubicin and 5.7 months with topotecan (P=0.047). Grade 3 or higher hematologic complications were significantly lower in the amrubicin group including neutropenia (41% *vs.* 54%), thrombocytopenia (21% *vs.* 54%), anemia (16% *vs.* 31%), and rates of blood transfusion (32% *vs.* 53%). Infections (16% *vs.* 10%) and febrile neutropenia (10% *vs.* 3%) were higher with amrubicin. Amrubicin has comparable activity, but higher toxicity compared to topotecan in patients with SCLC, with intriguing activity in patients with platinum-refractory SCLC. Amrubicin is currently approved in Japan as a second-line therapy for relapsed SCLC patients.

Irinotecan

Irinotecan, a topoisomerase I inhibitor, is another active agent against SCLC (35). A phase II trial studied irinotecan at 100 mg/m^2/day (on days 1, 8 and 15), given every 4 weeks in 16 patients with relapsed or refractory SCLC (36). It reported a RR of 47%, median time to disease progression of 58 days, and an OS of 187 days. Two separate phase II trials explored a higher dose of irinotecan (300 mg/m^2 given in 3-week intervals) in patients with relapsed SCLC (n=46 and n=65) but only 17–21% of patients achieved PR or stable disease (37,38). The median time to tumor progression in these studies was 11 weeks, while OS was 4–13 months. Grade 3–4 adverse effects

included neutropenia (21%), thrombocytopenia (10%) and diarrhea (13%).

Another phase II trial tested irinotecan at a dose of 100 mg/m^2/day on days 1 and 8 (in 21-day cycles) in 30 patients with sensitive (n=18) or refractory (n=12) relapsed SCLC (39). RR was 41.3% (61% in sensitive relapse and 9% in refractory relapse). Median PFS was 4.1 months overall, 5.2 months in patients with a chemotherapy-sensitive relapse and 2.1 months with refractory relapse (P<0.05). Median OS was 10.4 months. The most common grade 3+ toxicities were neutropenia (36.7%), leukopenia (16.7%), anemia (13.3%) and thrombocytopenia in (3.3%). The most common grade 3+ non-hematologic toxicities included diarrhea (10%), anorexia (6.6%), fever (6.6%), and hyponatremia (6.6%). The results showed a better response in patients with sensitive relapse, as well as fewer missed doses and less treatment delay.

Trials studying irinotecan combinations with etoposide (40) or gemcitabine (41) showed modest activity in the second-line setting as well. Irinotecan (70 mg/m^2 IV on days 1, 8, and 15) plus etoposide (80 mg/m^2 intravenously on days 1 to 3) showed a RR of 71% in 25 patients with relapsed SCLC. The median response duration was 4.6 months and median survival was 271 days. Major toxicities were myelosuppression [Grade 3–4 neutropenia (56%) and thrombocytopenia (20%)] and diarrhea (Grade 3–4, 4%). A phase II trial tested gemcitabine (1,000 mg/m^2) and irinotecan (100 mg/m^2 on days 1 and 8) in 21-day cycle, in 35 patients. Outcomes were modest, with a RR of 17%, median OS of 5.8 months and a 1-year survival rate of 34%.

A liposomal formulation of irinotecan (nal-IRI) is also in development (42). Liposomal irinotecan was explored in a single arm, dose finding phase II trial for patients with SCLC that had progressed after first-line platinum-based therapy. Patients received liposomal irinotecan 85 mg/m^2 or 70 mg/m^2 via intravenous infusion every 2 weeks. The dose of 70 mg/m^2 was chosen for expansion. Initial reports from 30 patients (25 of whom were treated at 70 mg/m^2) noted a response rate of 43.3%. Grade 3 and higher treatment emergent adverse events were observed in 40% of patients at the 70 mg/m^2 dose including 20% with diarrhea, 16% neutropenia, 8% anemia, and 8% thrombocytopenia. A phase III trial comparing liposomal irinotecan with second line topotecan is ongoing.

Temozolomide

Temozolomide is an orally bioavailable alkylating agent that produces O^6-alkyl-guanine lesions on DNA, inducing apoptosis in tumor cells. It has shown efficacy in SCLC (43). A phase II trial explored temozolomide 75 mg/m^2 per day, given for 21 days in a 28-day cycle, in patients with relapsed SCLC (48 with platinum-sensitive and 16 with platinum-refractory relapse) (44). The RR was 23% in patients with platinum-sensitive relapse and 13% in the refractory subset. Patients with asymptomatic, untreated brain metastases were included and among the 13 patients with target lesions in the brain, 4 patients achieved a CR, and another had a partial response for an overall response rate in the brain of 38%. The trial also reported a higher RR in patients with methylated *MGMT* compared to those with unmethylated *MGMT* (38% versus 7%), but this did not reach statistical significance (P=0.08). The median PFS was 3.5 months. Grade 3+ hematologic toxicities in patients included lymphopenia (30%), thrombocytopenia (10%), neutropenia (5%) and anemia (3%). Grade 3+ non-hematologic toxicities included fatigue and rash (both 3%). Due to the prolonged myelosuppression seen with this schedule, a modified regimen was explored with temozolomide given at 200 mg/m^2 per day, for 5 consecutive days in 28-day cycles (45). A trial using this regimen included 25 patients with relapsed SCLC. The RR was similar to the previous trial at 12% with comparable rates of hematologic adverse effects including Grade 3–4 thrombocytopenia (16%), neutropenia (8%), anemia (4%).

Targeted therapy

While targeted therapy has transformed the therapeutic landscape of non-small cell lung cancer (NSCLC), the paradigm has yet to impact SCLC. This is in large part due to the lack of activated oncogenic drivers. Genomic analyses of SCLC have been characterized by frequent loss of tumor suppressor genes *RB1* and *TP53* (7,46) and amplification of the *MYC* proto-oncogene which are challenging to leverage from a therapeutic standpoint (47). Still, there are several targets that may prove important in the treatment of SCLC and as our collective understanding of SCLC biology improves, there will certainly be more to come (48).

PARP

Poly (ADP-ribose) polymerase (PARP) is a DNA repair protein highly expressed at the mRNA and protein levels in SCLC that has emerged as a candidate therapeutic target (49). PARP acts as a co-activator for E2F1 leading to

production of E2F1-regulated DNA repair proteins. PARP inhibition acts by either directly blocking the repair of double-strand DNA breaks or by inhibiting the expression of E2F1-regulated DNA repair proteins, which can impair DNA repair and potentially enhance the efficacy of other therapies that induce double-strand DNA breaks (50).

Talazoparib is an active PARP inhibitor that was studied in a phase I study in patients with germline mutations in *BRCA1/2* and select sporadic cancers (51). This study included 23 patients with advanced SCLC who received talazoparib at a dose of 1 mg daily. Two patients, both of whom relapsed within 6 months of receiving platinum therapy, achieved a response; the overall response rate was 9% lasting 12.0 and 15.3 weeks. Including 4 patients with stable disease lasting at least 16 weeks, the clinical benefit rate was 26%.

A phase I/II trial studied the combination of the PARP inhibitor olaparib with temozolomide in 48 patients with previously treated SCLC (52). The RR was 41.7%, median PFS was 4.2 months, and median OS was 8.5 months. A randomized phase II study tested the impact of adding the PARP inhibitor veliparib to temozolomide in patients with recurrent SCLC (53). The RR was significantly better in the temozolomide plus veliparib group at 39%, compared to 14% with temozolomide plus placebo (P=0.016). There was no difference, however, in the 4-month PFS rate (36% with veliparib and 27% with placebo, P=0.19) or in median OS (8.2 months with veliparib *vs.* 7.0 months with placebo, P=0.5). Grade 3–4 thrombocytopenia (50% *vs.* 9%) and neutropenia (31% *vs.* 7%) were more common with temozolomide plus veliparib compared to temozolomide plus placebo. The study evaluated several biomarkers including expression of PARP-1 and SLFN11 by immunohistochemistry and methylation of the *MGMT* promoter. The investigators observed among patients receiving temozolomide plus veliparib, those with SLFN11-positive tumors had a significantly prolonged PFS (5.7 *vs.* 3.6 months; P=0.009) and OS (12.2 versus 7.5 months; P=0.014) compared to patients whose tumors did not express SLFN-11. In the temozolomide plus placebo group, there was no impact on PFS or OS by SLFN11 expression. There was no correlation between clinical outcomes and either PARP-1 expression or *MGMT* promoter methylation (54).

PARP inhibition may also play an immunomodulatory role in the treatment of SCLC. A study reported DNA damage response (DDR) protein [PARP and checkpoint kinase 1 (CHK1)] inhibition significantly increased the expression of programmed cell death ligand 1 (PD-L1), potentiating PD-L1 blockade, augmenting cytotoxic T-cell infiltration and inducing tumor regression *in vivo* (55). DDR inhibition also activated the STING/TBK1/IRF3 innate immune pathway, which also leads to activated cytotoxic T-lymphocytes. This has yet to be validated clinically.

Delta-like protein 3 (DLL3)

DLL3 is a NOTCH protein expressed in about 80% of SCLC tumor cells (56). DLL3 is an appealing target due to its high expression in the SCLC cells and minimal to no expression in normal tissues. Rovalpituzumab Tesirine (Rova-T) is an investigational antibody-drug conjugate that targets DLL3. A phase I trial studied Rova-T in patients with progressive SCLC or large-cell neuroendocrine tumors previously treated with one or two chemotherapy regimens (56). The recommended phase 2 dose was established as 0.3 mg/kg every 6 weeks. An objective response was seen in 18% (11/60) of the patients, 10 of whom had high DLL3 expression (>50%). Grade 3 or higher toxicities were seen in 38% of the patients including Grade 3–4 thrombocytopenia in 11% and pleural effusion in 8%.

A phase II study (TRINITY) assessed Rova-T in patients with DLL3-expressing SCLC who had received two or more prior lines of treatment (57). A total of 339 patients were treated with Rova-T at 0.3 mg/kg, every 6 weeks for two doses, with retreatment permitted upon progression. Rova-T achieved a low RR of 12% and a median OS of 5.6 months in all patients. Outcomes were not significantly better in patients with higher DLL3 expression. Grade 5 fatal adverse events were seen in 10% of patients and Grade 3–4 events were observed in an additional 53%, including thrombocytopenia (11%), photosensitivity (7%), and pleural effusions (4%). Additional studies investigating Rova-T also had disappointing outcomes. A phase III trial (TAHOE) that randomized patients to Rova-T versus topotecan was stopped early due to the inferior OS with Rova-T. Another phase III trial (MERU- NCT03033511) investigating Rova-T as maintenance therapy following the first-line chemotherapy was terminated due to lack of survival benefit at the pre-planned interim analysis (58).

Despite the disappointment seen with Rova-T, DLL3 remains an appealing target and other strategies to leverage DLL3 expression are ongoing. These include a DLL3-targeted bispecific T cell engager (BiTE®) and chimeric antigen receptor (CAR) T cell therapy (59). AMG 757 is an anti-DLL3-CD3 BiTE® antibody shown to induce cell

death in DLL3-positive cancer cells (60) and inhibit tumor growth in SHP-77 SCLC xenograft model *in vivo* (61). AMG 119 is a genetically modified autologous T-cell that also targets DLL3 and triggers T cell-mediated cytotoxicity and tumor cell death (60,61). Preclinical data suggest that AMG 119 may have high potency and specificity for DLL3-positive SCLC tumor cells. Both of these DLL3 targeted agents are being investigated in phase I trials [NCT03319940 (62), NCT03392064 (63)] to assess their safety, efficacy and toxicity.

Gefitinib

The epidermal growth factor receptor (EGFR) pathway represents an important therapeutic target in several tumors including NSCLC (64). This pathway is not frequently engaged in SCLC (65). Gefitinib, an oral EGFR tyrosine kinase inhibitor, did show efficacy in some cell lines with low EGFR expression, prompting study in relapsed SCLC (66). A phase II trial of gefitinib in 19 patients with SCLC showed no meaningful efficacy (67). Seventeen patients had progressive disease with a median time to progression of 50 days and a 1-year OS rate of 21%. This agent is not in active development for the treatment of SCLC.

Bevacizumab

Bevacizumab is a vascular endothelial growth factor (VEGF) monoclonal antibody currently indicated for patients with several cancers, including NSCLC (68). VEGF stimulates angiogenesis in tumors, and high levels of VEGF correlate with chemotherapy resistance and poor survival in patients with SCLC (69). Multiple trials exploring bevacizumab with chemotherapy, as maintenance treatment, or alternating with chemotherapy in patients with previously untreated SCLC patients did not show any substantial difference in efficacy (70-74).

A phase II trial assessing the efficacy of paclitaxel and bevacizumab in platinum-sensitive relapsed SCLC (RFI ≥60 days) did not show substantial clinical activity (75). A total of 33 patients received paclitaxel at 90 mg/m^2 (IV) on days 1, 8 and 15 and bevacizumab at 10 mg/kg (IV) on days 1 and 15, both in 28-day cycles. RR was 18%, PFS was 15 weeks and median OS was 30 weeks. Grade 3+ toxicities included fatigue (26%), neutropenia (17%), and dyspnea (15%). This trial also studied VEGF polymorphisms in 30 patients as potential predictive markers but reported no statistically significant association between specific polymorphisms and response to bevacizumab. Another multi-center phase II trial studied a combination of paclitaxel and bevacizumab in 30 patients with chemotherapy-resistant relapsed SCLC (RFI <90 days) (76). Enrolled patients were heavily pretreated; 63% had received at least two prior lines of treatment. The RR was 20%, PFS was 2.7 months, median OS was 6.3 months and 1-year OS rate was 25%. Grade 3–4 toxicities included leukopenia (20%), neutropenia (17%) and diarrhea (10%).

Immunotherapy

Immunotherapy is the standard of care for many cancers characterized by high tumor mutational burden (TMB) such as NSCLC, melanoma and bladder cancer (77-79). This supported exploration of immunotherapy in the treatment of SCLC, a carcinogen-related tumor characterized by high TMB (80). While initial studies showed promise, the activity of checkpoint inhibitors in an unselected population was modest. Furthermore, with the evolving standard of care that now implements PD-L1 inhibition in the first-line setting, the role of checkpoint-inhibitors in patients who had previously received immunotherapy is unclear. There is no convincing evidence to date that these strategies will be effective, but more studies, particularly with immunotherapy combinations, are warranted. Still, based on the lack of options available at the time, and primarily relevant to an immunotherapy naïve patient population, checkpoint inhibitors were approved as third line monotherapy for relapsed SCLC (*Table 2*) based on durable, meaningful responses that were observed in a subset of patients

Nivolumab with or without Ipilimumab

CheckMate 032 was a multi-center, open-label, phase I/II trial evaluating the PD-1 inhibitor nivolumab alone or with the CTLA-4 inhibitor ipilimumab in patients with previously treated (though immunotherapy-naïve) SCLC (83). In the initial non-randomized portion of this study, 216 patients with relapsed SCLC were treated with nivolumab alone or nivolumab with ipilimumab in various dosing schedules (*Table 3*). Nivolumab monotherapy was associated with a relatively low response rate (10%). Patients receiving nivolumab plus ipilimumab achieved higher response rates (19–23%) but also had a higher rate of grade 3 or higher adverse events. An important clinical outcome was the relatively robust landmark survival rates

Table 2 Summary of outcomes for SCLC with third line anti-PD-1 monotherapy

Author	Therapy	Patients (n)	RR	Responses Ongoing at 1 year	Median PFS (months)	Median OS (months)	OS Rate at 1 year	Grade 3+ TRAE
Ready (81)	Nivolumab	109	11.9%	61.5%	1.4	5.6	28.3%	11.9%
Chung (82)	Pembrolizumab	83	19.3%	67.7%	2.0	7.7	34.3%	9.6%

OS, overall survival; PFS, progression free survival; RR, response rate; TRAE, treatment related adverse event.

Table 3 Outcomes of non-randomized portion of CheckMate 032 (79)

	Nivolumab (3 mg/kg) every 2 weeks	Nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) every 3 weeks for four cycles, then nivolumab maintenance	Nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every 3 weeks for four cycles, then nivolumab maintenance
Patients (n)	98	61	54
RR (%)	10	14	10
Median PFS (months)	1.4	2.6	1.4
Median OS (months)	4.4	7.7	6.0
One-year OS rate (%)	33	43	35
Grade 3–4 TRAE (%)	13	30	19

Ipi, ipilimumab; Nivo, nivolumab; OS, overall survival; PFS, progression free survival; RR, response rate; TRAE, treatment related adverse event

observed in this heavily pretreated population. The 1-year survival rate with nivolumab alone was 33% and 35–43% with the combination of nivolumab and ipilimumab.

An expansion cohort of CheckMate 032 randomized 242 patients 3:2 to nivolumab monotherapy (3 mg/kg every 2 weeks; n=98) versus nivolumab plus ipilimumab (nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks x 4 followed by nivolumab 3 mg/kg maintenance every 2 weeks; n=61) (84). Outcomes were comparable to the non-randomized portion. The RR was 11% in the nivolumab group and 25% with nivolumab plus ipilimumab, and the 1-year OS rates were 30% and 42%, respectively. Responses were independent of the PD-L1 expression or platinum-sensitivity. Grade 3–4 adverse effects were seen in 14% of patients in the nivolumab group and 33% of patients in the combination group.

In the subset of 109 patients across CheckMate 032 (both the non-randomized and randomized cohorts) who received nivolumab monotherapy as third-line or later, there was promising activity, particularly considering the lack of alternate options (*Table 2*). In these patients, the RR to third-line nivolumab was 11.9% with a median duration of response of 17.9 months (81). Grade 3–4 treatment related adverse events were seen in 12% of patients. Based on this activity, the Food and Drug Administration (FDA) granted accelerated approval to nivolumab monotherapy in the third-line setting for advanced SCLC on August 16, 2018.

An effort to introduce immunotherapy in the second-line setting was unsuccessful. A phase III trial (CheckMate 331) compared nivolumab monotherapy to chemotherapy (topotecan or amrubicin) in 567 patients with relapsed SCLC (85). Nivolumab did not improve survival. Median OS was 7.5 months with nivolumab and 8.4 months with chemotherapy (HR, 0.86; 95% CI, 0.72–1.04, P=0.11). The RR was comparable at 14% with nivolumab versus 16% with chemotherapy. The PFS was 1.4 months with nivolumab and 3.8 months with chemotherapy (PFS HR 1.41; 95% CI, 1.18–1.69). Maintenance immunotherapy was similarly disappointing. In CheckMate 451, 834 patients with at least stable disease after 4 cycles of platinum-based chemotherapy were randomized to receive nivolumab monotherapy, nivolumab with ipilimumab, or placebo (86). Nivolumab plus ipilimumab did not improve survival over placebo, which was the primary endpoint. Patients who received nivolumab plus ipilimumab had a median PFS of 1.7 months, a median OS of 9.2 months, and a 1-year OS rate of 41%. Patients treated with placebo had a median PFS of 1.4 months, a median OS of

9.6 months, and a 1-year OS rate of 40%. Outcomes with nivolumab monotherapy were comparable. Median OS with nivolumab monotherapy was 10.4 months, compared to 9.6 months with placebo (HR 0.84; 95% CI, 0.7–1.0).

Pembrolizumab

KEYNOTE-028, a phase Ib trial, investigated the PD-1 inhibitor pembrolizumab (10 mg/kg, every 3 weeks) in patients with immunotherapy naïve, relapsed SCLC. Eligible patients had tumors with at least 1% of cells expressing PD-L1. In 24 patients, the response rate was modest but landmark survival was encouraging (87). The RR was 33% and the median PFS was 1.9 months, but the median OS was 9.7 month and the median duration of response was 19.4 months. The 6-month OS rate was 66% and the 1-year OS rate was 38%.

A phase II trial (KEYNOTE-158) investigated pembrolizumab (200 mg every 3 weeks) in patients with relapsed SCLC, with no PD-L1 tumor selection (82). A pooled analysis allowed examination of pembrolizumab as third-line therapy (*Table 2*) (88). In 83 patients, the RR was 19.3% and as seen with nivolumab, responses were durable. While the median duration of response was not reached, 61% of responders had responses ongoing at 18 months. The median PFS was modest at 2 months with a median OS of 7.7 months but landmark survival rates were more impressive, with a 24-month OS rate of 20.7%. Grade 3 treatment-related adverse events were noted in 7.2% with no grade 4 adverse events and two fatal treatment related adverse events. Pembrolizumab also received accelerated FDA approval in the third-line setting based on these encouraging data.

Atezolizumab

Atezolizumab is a PD-L1 antibody that also has efficacy in SCLC. In the global, randomized, phase III IMpower133 trial, the addition of atezolizumab to standard first line carboplatin plus etoposide led to significant improvements in PFS and OS (4). This was the first intervention to impact survival in treatment naïve SCLC, leading to the FDA approval of atezolizumab on March 18, 2019 as part of the first-line treatment for ES-SCLC. In contrast, the role of atezolizumab for relapsed SCLC is limited. An IFCT phase II trial evaluated atezolizumab or chemotherapy as second-line therapy in 73 patients with immunotherapy naïve, relapsed SCLC and reported disappointing outcomes (89). Atezolizumab in this setting had a RR of only 2.3% with a median PFS of 1.4 months and a median OS of 9.5 months. The phase III portion was not activated and the current role of atezolizumab in SCLC is only as part of first-line therapy.

Conclusions

SCLC is an aggressive and unforgiving disease with a high relapse rate making salvage therapy important for almost all patients. There are many active cytotoxic agents, most characterized by a modest RR and short survival. Topotecan and lurbinectedin are currently the only approved second-line agents in the US, with limited efficacy and notable toxicity. Pembrolizumab and nivolumab are welcome additions to the treatment armamentarium as the only third-line agents with FDA approval but in the current therapeutic landscape, delivery of immunotherapy as first-line therapy remains best practice. Resistance to therapeutic interventions remains the primary challenge. While immunotherapy has improved outcomes, particularly in the first-line setting, both primary and acquired resistance have been difficult to overcome. Downregulation of major histocompatibility complex class I molecules, impaired infiltration of lymphocytes into tumors and active immune suppression from myeloid-derived suppressor cells have all been described as mechanisms of resistance to immunotherapy in SCLC (90). Similarly, cytotoxic agents often are capable of inducing responses but resistance emerges quickly. Resistance mechanisms are diverse and include alterations of DNA (methylation, glutathione), RNA (microRNAs), apoptosis, and metabolism, among others (91). However, much of this data is based on preclinical models and the heterogeneity of drug resistance demands in depth analyses of serial biopsies which are particularly challenging to retrieve in patients with advanced SCLC. Still, this is what is required to develop novel agents to manage this highly lethal disease and continue to improve patient outcomes.

Acknowledgments

Funding: None

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Alfredo Addeo and Giuseppe Banna)

for the series "Non-Small Cell Lung Cancer" published in *Precision Cancer Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/pcm-20-24

Peer Review File: Available at http://dx.doi.org/10.21037/pcm-20-24

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/pcm-20-24). SVL reports advisory board/consultant fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, G1 Therapeutics, Genentech/Roche, Guardant Health, Janssen, Lilly, LOXO, Merck/MSD, PharmaMar, Pfizer, Regeneron, Takeda and research (grant) funding (to institution) from Alkermes, AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Corvus, Genentech, Lilly, Lycera, Merck, Molecular Partners, Pfizer, Rain Therapeutics, RAPT, Spectrum, and Turning Point Therapeutics. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pcm-20-24
Cite this article as: Farid S, Liu SV. A narrative review of salvage therapy in small cell lung cancer. Precis Cancer Med 2020;3:20.