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REVIEW

SMALL CELL LUNG CANCER IN THE ERA OF IMMUNOTHERAPY

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ABSTRACT

Small cell lung cancer, accounting for approximately 14% of lung cancer cases, remains one of the most aggressive malignancies. Despite its lower incidence compared to non-small cell lung cancer, its early metastasis and rapid progression make small cell lung cancer a major public health concern due to poor survival outcomes. Five-year survival rates remain below 7% for extensive-stage disease, highlighting the urgent need for improved diagnostic and therapeutic strategies. Although epidemiologically small cell lung cancer is considered less hazardous than in previous decades, it continues to pose a substantial global public health burden. Changes in epidemiology include a narrowing of the historical male predominance, regional variations, and higher age-standardized incidence rates in Eastern Asia, Micronesia, Polynesia, Northern Europe, and North America. Although long-term survival remains limited, significant improvements with modern treatment options have been reported. Platinum-based chemotherapy combined with etoposide remains the first-line standard for both limited-stage and extensive-stage small cell lung cancer. Thoracic radiotherapy, prophylactic cranial irradiation to reduce the risk of brain metastases, and surgery for highly selected early-stage patients are among current treatment modalities, alongside second-line therapies such as topotecan. In parallel, novel therapeutic approaches primarily immunotherapies and patient-specific targeted therapies are showing substantial promise. The use of immune checkpoint inhibitors in combination with chemotherapy has been shown to improve survival in extensive-stage small cell lung cancer. Furthermore, integration of bispecific T-cell engagers targeting delta-like canonical Notch ligand 3, antibody-drug conjugates, poly-adenosine diphosphate ribose polymerase inhibitors, and epigenetic modulators with existing treatment strategies represents a promising direction for future therapy. Despite challenges including small trial sizes, resistance mechanisms, and treatment-related toxicity, these approaches may become more widely used in clinical practice. Overall, small cell lung cancer remains a serious clinical challenge that requires continued development of novel treatment strategies. These emerging approaches hold significant potential for providing more patient-specific therapeutic options. Ongoing and future clinical trials will be critical for establishing effective treatment algorithms and improving long-term outcomes in patients with this aggressive cancer. In this context, immunotherapy has emerged as a cornerstone of modern small cell lung cancer management, particularly in extensive-stage disease. Understanding the biological basis of immunotherapy responsiveness and resistance is therefore essential for optimizing current and future treatment strategies.

Keywords: Immunotherapy, prognosis, small cell lung carcinoma, therapeutics

INTRODUCTION

Lung cancer is the leading cause of cancer death in both men and women, being responsible for a quarter of all cancer deaths. Five-year survival is 59.0% for localized disease at diagnosis, and it decreases to as low as 5.8% for those with metastatic disease. Regarding that 57% of lung cancer cases in the United States are diagnosed after metastasis (1, 2), lung cancer poses a great danger to public health all around the world (1, 3). As a result, it is important to understand the classification and fundamentals of the disease (3, 4). It is divided into two main histological types: small cell lung cancer (SCLC) and non-SCLC (NSCLC) (Figures 1 and 2). According to the World Health Organization Classification of Tumors, SCLC is characterized by small, round-to-fusiform cells with scant cytoplasm, finely granular chromatin, and inconspicuous nucleoli (1). As the two types have different clinical behaviour, they need to be analyzed separately as well as together in order to optimize treatment options for both (3, 5). Although SCLC has a lower incidence compared to NSCLC, it is stated as the most aggressive type, which makes it important to specifically focus on it (5-7). Another aspect that should be examined is that given the limited durability of responses

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achieved with conventional chemotherapy and radiotherapy, immunotherapy has gained increasing attention as a strategy to improve long-term disease control. The integration of immune checkpoint inhibitors (ICI) into first-line treatment has marked a significant shift in the therapeutic landscape of SCLC (6, 7).

Epidemiology and Prognosis

Small cell lung cancer accounts for approximately 14% of all lung cancer cases, and it is expected to remain as a hazard to public health (6, 8, 9). Each year, nearly 250,000 patients are diagnosed with the disease, of which 200,000 are not able to overcome it (9). In 2019 global data, the disease is seen in females slightly more than males, with a difference of 5.1%. Although SCLC was seen dominantly in males in the past, due to the faster decrease of male patient cases, the male predominance of 68.3% in 1975 has changed through time. On the other hand, in females the incidence showed an increase until 1982 with a decreasing speed, and it started to decrease slowly afterwards (6, 9). Ancestry differences are present in SCLC cases as well with a notable difference from lung cancer cases in general. Despite the higher rate of lung cancer in general and the disadvantages of health service access, African ancestry is linked with a lower risk and higher survival rate of SCLC (8, 9). For both sexes, a high age-standardised incidence rate (ASIR) was seen in Eastern Asia, which states that the disease is seen at a higher rate regardless of the increase due to the increasing age. Additionally, a high ASIR was noted in Micronesia and Polynesia for males, in Northern Europe and Northern America for females (10). Regardless of age and sex, SCLC is still considered a public health danger and burden despite the decreasing trend of the disease overall.

The clinical presentation of SCLC is highly variable and often non-specific. The most frequently reported symptoms include cough, which is observed in approximately 40% of patients, and dyspnea, which occurs in around 34% of cases (Figure 3). Hemoptysis is less common, affecting roughly 10% of patients, yet it remains a notable presenting feature. Importantly, a substantial proportion of patients, estimated to be as high as 60%, may remain asymptomatic at the time of diagnosis, which contributes to delays in detection and initiation of therapy (11, 12). This silent clinical course is one of the major reasons why SCLC is typically diagnosed at an advanced stage. Nearly 70% of patients present with extensive-stage disease at initial diagnosis, underscoring the aggressive biology and rapid progression that characterize this malignancy (11, 13). Paraneoplastic syndrome (PNS) can also be existent in some cases of SCLC. Endocrinologic and neurological PNS are stated clinically with a significant amount alongside SCLC. SCLC is also one of the types of malignancies most strongly linked with PNS. Overall, the paraneoplastic entities associated with SCLC represent a complex interplay between ectopic hormonal secretion and immune cross-reactivity. This adds to the fatality and importance of possible treatments for SCLC. SCLC, which is strongly linked with smoking and tobacco carcinogens, is seen also as one of the most aggressive forms of cancer with a high capacity for metastasis (11, 12, 14, 15). Furthermore, use

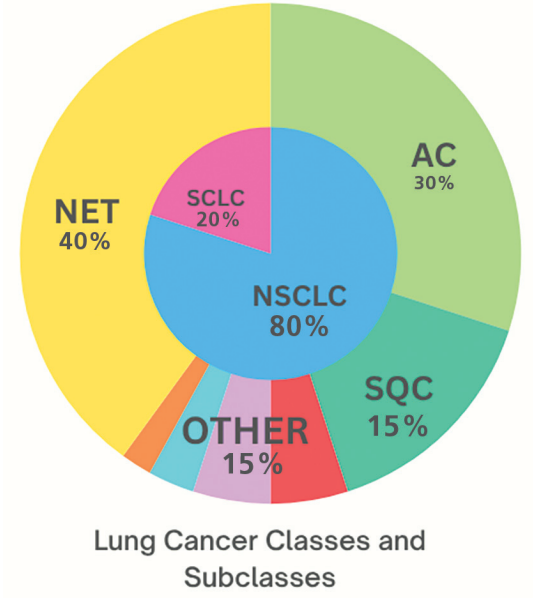

Figure 1: Showing the incidence of lung cancer classes and subsclasses. While adenocarcinoma and squamous cell carcinoma are mostly seen as subclasses under the class of only non-small cell lung cancer, the most common subtype neuroendocrine tumors can be considered both small cell lung cancer and NSCLC (9-11).
AC: Adenocarcinoma, SQC: Squamous cell carcinoma, NSCLC: Non-small cell lung cancer, NET: Neuroendocrine tumors, SCLC: Small cell lung cancer

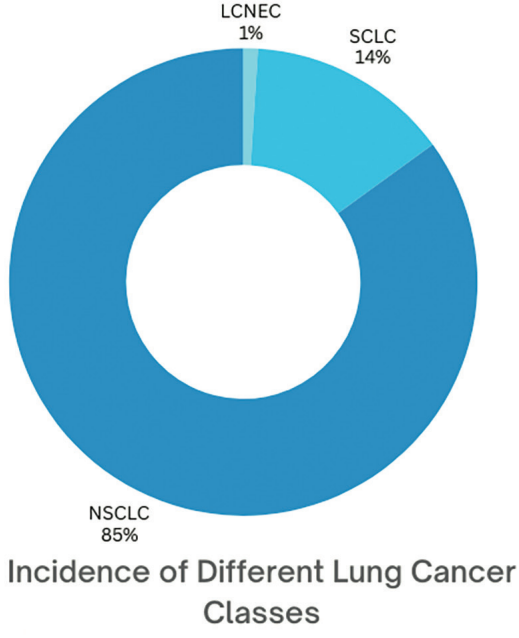

Figure 2: Showing the incidence pie chart of small cell lung cancer classes where non-small cell lung cancer is the most common type. Large cell neuroendocrine carcinoma corresponds to another class that is a minority compared to the other two sub-types (8, 10, 11).
NSCLC: Non-small cell lung cancer, SCLC: Small cell lung cancer, LCNEC: Large cell neuroendocrine carcinoma

of tobacco can negatively impact the survival factors of the disease and it can make it harder for patients to get positive results from the treatments. The potential effects of tobacco use can be listed as genetic and epigenetic effects and chronic inflammatory responses which all combine to explain the aggressive biological behavior of SCLC and its tendency for early dissemination (12-15).

Even though SCLC is defined as a form of lung cancer with poor prognosis, it is seen that the prognosis of some SCLC cases was improving (14, 16). An increase in median age at diagnosis from 63 to 69 years and an improvement in five-year overall survival (OS) were also stated (16, 17). Specifically, one-year and five-year OS rates improved from 23% and 3.6% in 1975-1979 to 30.8% and 6.8% in 2010-2019 (17). A significant decrease in the incidence of the disease was stated as well, with a closer male-female ratio and a higher OS rate (18). These epidemiological shifts are largely attributed to declining smoking rates, reinforcing the well-established causal link between tobacco use and SCLC (15, 19). Advances in medical technology have contributed to reductions in incidence-based mortality; however, more effective systemic therapies are still needed to achieve substantial improvements in survival outcomes (19).

Low-Dose Computed Tomography for Lung Cancer Screening

Lung cancer, with its close association to smoking, is the leading type of cancer. Causing the majority of cancer mortalities, new methods to early-diagnose lung cancer have been subjected to trials. Previous randomized trials involving chest radiography and sputum analysis have shown no mortality reduction (18). However, low-dose computed tomography (LDCT) has allowed for a non-invasive, high resolution and practical screening test to be implemented. Due to the radiation exposure involved only people at high-risk are considered to be screened. The definition of high-risk, with little difference from guideline to guideline, is heavy-smokers aged 55 to 74 years of age who have a history of 30 pack-years of smoking. Former smokers who quit in the previous 15 years are also considered high-risk (20).

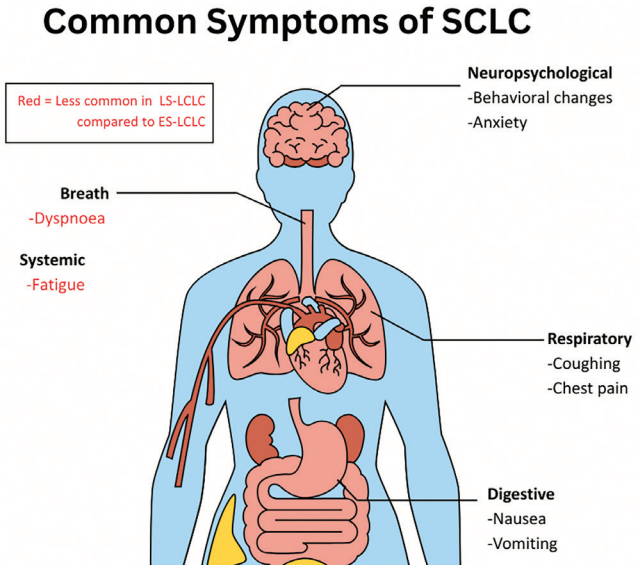

Figure 3: Showing signs and symptoms of small cell lung cancer. Symptoms written in red indicate symptoms that are more common in extensive stage compared to limited stage SCLC. Cough and dyspnoea were reported as the most common ones overall (12-15).
SCLC: Small cell lung cancer, LS: Limited stage, ES: Extensive stage, LCLC: Large cell lung carcinoma

A trial involving 12,773 participants (https://pubmed.ncbi.nlm.nih.gov/36428100/), was conducted to test the performance of a screening test. It had a high sensitivity and a low false positive rate. Most lung cancers were stage I or II with the majority being the stage I. This trial proved that screening can improve early detection in lung cancer. However, the SUMMIT trial could not evaluate the rate of overdiagnosis due to not having an unscreened control group (21). Overdiagnosis is an important aspect of screening. Treating a dormant or slow-growing cancer which won't be clinically significant in patients lifetime causes unnecessary and unwanted results (22).

The National Lung Screening Trial (https://clinicaltrials.gov/study/NCT00047385) conducted from August 2002 to 2004 had 53,454 participants which were considered high-risk for lung cancer. This study compared screening efficiency of chest radiography with LDCT. There were three screenings one year apart. Non-calcified nodules bigger than 4 mm were considered suspicious for lung cancer. The percentage of early stage cancers were higher in this study as well. In the LDCT group mortality rates were 20.0% lower than the radiography group but also LDCT had a higher rate of false positive results. SCLC had a lower detection rate compared to NSCLC by either screening procedure (23). Recently another study analyzing SCLC patients diagnosed at the Henry Ford Health System revealed that screen-detected patients had a considerably better OS rate (24). Ongoing trials will show if the benefits of LDCT screening outweighs its disadvantages.

Classification of Small Cell Lung Cancer

The Veterans Administration of Lung Study Group (VALSG) and the tumour, node, metastasis (TNM) staging of the American Joint Committee on Cancer are both used to classify SCLC. VALSG categorizes the disease as limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC) (25). TNM staging assesses the disease by the following: primary tumor (T), nodal involvement (N), and distant metastasis (M) (26).

If the disease is restricted to a single hemithorax and can be safely enclosed in one radiation field, it is considered to be limited. If the disease presents with malignant effusions of the pleura or the pericardium, or has spread beyond a single hemithorax, it is considered to be extensive (25). According to the 8th edition of TNM staging of lung cancer, T is assessed under the following categories: Tx, T0, Tis, T1 (T1a, T1b, T1c), T2 (T2a, T2b), T3, and T4. A tumor is considered Tx when the tumor does not show up in radiological or bronchoscopical

examination, but is evident in histopathological examination. T0 is defined as the absence of evidence of a primary tumor, and Tis refers to carcinoma in situ. Primary tumors are categorized into T1, T2, T3, and T4 stages based on their size, location, invasions of adjacent structures, and separate tumor nodules. Lymph nodules are assessed similarly and are categorized as the following: Nx, N1, N2, N3. If the lymph nodes are not suitable for assessment, the disease is Nx, and if there is no lymph node involvement, the disease is N0. N1, N2, and N3 stages are categorized depending on which nodules are involved. Distant metastasis is only divided as M0 and M1, no distant metastasis and the presence of it, respectively. Depending on how the patient presents in T, N, and M, they are diagnosed with stages from I to IV (26). Patients with stages I-III and suitable for curative intent therapy are equivalent to LS-SCLC, and stage III patients not suitable for curative intent treatment or stage IV patients are equivalent to ES-SCLC (27).

Chemotherapy in Small Cell Lung Cancer

For both LS-SCLC and ES-SCLC patients, platinum-based chemotherapy with the regimens cisplatin-etoposide or carboplatin-etoposide is recommended as a part of the first-line treatment (27). Although previously other regimens were used, a meta-analysis of 4,054 patients that compared the effectiveness of cisplatin versus non-cisplatin regimens concluded that the use of cisplatin regimens resulted in higher survival and response rates while not increasing toxicity (28). The effectiveness of cisplatin and carboplatin in patients diagnosed mainly with ES-SCLC was compared by Rossi et al. (29). Analysis revealed that both treatment arms had balanced OS, overall response rate (ORR), and progression-free survival (PFS) values. Hematologic toxicities were more common in the carboplatin arm, and non-hematologic toxicities were more common in the cisplatin arm, making the regimens' toxicity profiles an important deciding factor when administering these drugs (29). Another retrospective analysis concluded that cisplatin and carboplatin resulted in similar median OS for both ES-SCLC and LS-SCLC patients regardless of performance status. In LS-SCLC patients, the effectiveness of these drugs did not differ based on stage, and in both studies carboplatin was associated with better survival in older ES-SCLC patients (29, 30).

Role of Surgery in Small Cell Lung Cancer

When selecting patients for surgical resection, TNM staging is found to be of use (1). Although there is conflicting data when it comes to the benefit of surgery in SCLC, for a limited group of patients (T1T2N0), surgery with multimodality treatment may be recommended as a treatment option (Figure 4) (27). In a retrospective trial with propensity score matching, surgery was found to improve OS in all subgroups included, and it lacked significance only for the stage II subgroup. This improvement was especially seen in stage I and T1/T2N0 groups. They also found that if an R0 margin was not achieved in surgery, the positive results for OS were lost. It is also important to note that stage I and stage IIIA surgical resection patients who did not undergo adjuvant chemotherapy and radiotherapy performed poorer than their non-surgical counterparts (31). A meta-analysis including the aforementioned study also found a consistent and significant OS benefit for surgery when retrospective studies conducted after 2004 were analyzed (32). Similar to the mentioned study, surgery without adjuvant therapy did not have an OS benefit, and in both trials, lobectomy was associated with better survival when compared to other surgical practices (31, 32).

Implementation of Thoracic Radiotherapy in the First Line Treatment of Small Cell Lung Cancer

In 1992, two meta-analyses concluded the addition of thoracic radiotherapy (TRT) to chemotherapy resulted in improved survival (33, 34). Pignon et al. (33) found that the addition of TRT led to a 5.4% increase in the three-year survival rates; similarly Warde and Payne (34) reported an improvement in the two-year survival rates by 5.4%.

To test fractioned TRT's effect on survival, concurrently with the first cycle of platinum-based chemotherapy, 45 Gy TRT was given to participants either once-daily (1.8 Gy daily in 25 treatments) or twice-daily (1.5 Gy in 30 treatments). Two- and five-year survival rates were assessed, and five-year survival showed 10% pro-TRT margin, although two-year rates were not deemed statistically significant (35). However, when twice-daily treatment schedules were implemented as split-course, two- and five-year OS and PFS rates did not show a statistically significant difference, yielding similar results to once daily treatments (36). Although in both of these studies grade 3 esophagitis rates were high and seen more in the twice-daily treatment arms, in more recent trials these rates were found to be lower due to the use of modern radiotherapy techniques and positron emission tomography/computed tomography (CT) staging (33-40).

The CONVERT trial was designed to show that 66 Gy once-daily treatments would result in higher OS rates in comparison to 45 Gy twice-daily treatments (37). However, not only the survival rates did not show significance, but also the two- and five-year OS rates showed a 5% (56% vs 51%) and 3% (34% vs 31%) margin in favor of twice-daily treatments, respectively. With the high survival rates, low toxicity rates, and the fact that the trial was not designed to test equivalence in mind, the authors concluded that twice-daily TRT should continue to be the standard therapy (37). Initiated in the same year with the CONVERT trial, CALGB 30610 was also designed to test if high-dose once daily (70 Gy in 35 Gy once-daily fractions over seven weeks) treatments are superior to standard-dose twice-daily treatments (45 Gy in 1.5 Gy twice-daily fractions over three weeks). Although both treatment arms had similar OS rates at two- and five- years, the data lacked statistical significance and failed to show the superiority of once-daily treatment (38). On the contrary, in a recent phase III trial, 54 Gy high-dose hyperfractioned radiotherapy resulted in higher median OS (60.7 months vs 39.5 months), median PFS (30.5 vs 16.7), and two-year OS rates (76% vs 54%) in comparison

to standard treatment (39). These results were in line with the previous phase II trial comparing 60 Gy hyperfractioned TRT and standard therapy (40).

As individual trials favored one or the other, earlier or shorter admission of TRT versus longer or later admission of TRT was also researched in a 2016 meta-analysis. If TRT was administered before both the third cycle of chemotherapy and nine weeks after randomization, it was considered as early TRT. When compared to later or longer TRT, three- and five-year OS rates favored earlier or shorter TRT by 5.7% and 7.7% in trials with similar chemotherapy compliance in both arms. In trials with different chemotherapy compliance in both arms, it was reported that earlier or shorter TRT decreased survival. Similar to OS, PFS at three- and five-years also increased with earlier or shorter TRT in trials with similar chemotherapy compliance in both arms. Both hyperfractioned accelerated TRT and cisplatin-based chemotherapy were found to be more beneficial when TRT was delivered earlier or shorter, but this treatment plan resulted in an increased cardiotoxicity, neutropenia, and esophagitis (41). In the study done by Sun et al. (42), late TRT (starting with the third cycle of chemotherapy) showed comparable results to early TRT (starting with the first cycle of chemotherapy) in terms of complete response rate, OS, and PFS, but it showed an increase in intrathoracic rates without statistical significance. In this analysis, neutropenia was associated more with the early TRT arm, similar to the meta-analysis by De Ruysscher et al. (41, 42). The integration of TRT to current ES-SCLC treatment strategies is actively being researched in ongoing clinical trials (43). MATCH, a phase II trial, revealed that LD-TRT (15 Gy in five fractions) in combination with chemoimmunotherapy resulted in an ORR of 87.5%. Patients who were responsive to chemoimmunotherapy had a higher median depth of response (DpR) when compared to the whole cohort. Patients who achieved PR with a DpR above the median DpR rate had better OS and PFS, the three-year OS rates showing a ~39% difference. LD-TRT treatment was deemed tolerable with only 10.7% of patients discontinuing treatment due to adverse events (AEs); however, the authors noted that another phase II trial on concurrent radiotherapy (30 Gy in ten fractions), TREASURE, had to stop recruitment due to an imbalance in AEs seen in treatment arms (44). Therefore, the optimal dosage and fractionation of concurrent TRT treatment should be further researched. TRT treatment following chemoimmunotherapy was associated with improved OS and PFS and was considered to be tolerable in a recent retrospective analysis (43). Median OS was 21.67 months and 16.6 months for TRT and non-TRT arms, and one- and two-year OS rates also favored TRT treatment. Although higher doses of TRT were associated with higher rates of pneumonitis, TRT was not found to significantly increase any grades of AEs (44).

In a retrospective trial, ES-SCLC patients treated with combined therapy had longer median OS (18.1 months vs 10.8 months) and better PFS (9.3 months vs 6.0 months) compared to chemotherapy alone. TRT received within the six cycles of chemotherapy resulted in better local recurrence free survival (45). After propensity score matching the results still favored combined therapy; the median OS and progression free survival was 16.4 months and 7.9 months for Chtr/TRT and 11.6 months and 6.5 months for chemotherapy alone (45).

Immunotherapy in Limited-Stage Small Cell Lung Cancer

Whether LS-SCLC patients can benefit from immunotherapy is also actively being researched. Interim analysis of the ongoing ADRIATIC trial revealed that adjuvant durvalumab treatment after chemoradiotherapy led to significantly longer OS and PFS when compared to placebo in LS-SCLC patients without disease progression after first-line treatment. The incidence of grade 3-4 AEs was similar in both groups. Durvalumab did have a 8% higher incidence of pneumonitis or radiation pneumonitis, but grade 3-4 rates of this AE were similar at 3.6% and 2.1% (46).

Implementation of Prophylactic Cranial Irradiation in the First Line Treatment of Small Cell Lung Cancer

Prophylactic cranial irradiation (PCI) is a therapy offered to SCLC patients who are responsive to first-line therapy (Figure 4) (27). According to a meta-analysis, at three years, the incidence of brain metastasis was reduced by 25.3% and survival was increased by 5.4% due to the administration of PCI to SCLC patients (47). In this analysis, it was concluded that an increase in the dose resulted in a higher treatment success (47). However, when a total of 25 Gy in ten fractions was compared to 38 Gy in either 18 or 24 fractions, the high-dose treatment arm not only showed no significant benefit in decreasing the two-year incidence of brain metastases, but also decreased OS at two years and increased the incidence of intrathoracic metastases at two years (48).

In 2007, Slotman et al. (49) reported a decreased risk of brain metastasis and an OS advantage observed in the irradiation arm in a study with ES-SCLC patients. However, a study conducted in Japan found that PCI in patients with ES-SCLC did not improve OS, as the median OS was 11.6 months for PCI patients and 13.7 months for the control group. They attributed the difference in these two trials' OS results to the absence of magnetic resonance imaging (MRI) scanning of patients who didn't have symptomatic brain metastases, which might have resulted in asymptomatic patients getting included in the previous trial. The incidence of brain metastasis was lower in the treatment arm which is in line with the previous studies. At 6, 12, and 18 months, the PCI group had 15%, 32.9%, and 40.1% incidences of brain metastasis, these percentages were 46.2%, 59.0% and 63.8% in the control group (50).

The landmark meta-analysis by Auperin et al. (47) was also conducted in the pre-MRI era, and due to the lack of MRI surveillance, it is possible that patients with brain metastasis prior to PCI were also included in this analysis (51, 52). In two more recent studies conducted on LS-SCLC patients, both a baseline MRI and a restaging surveillance

before PCI was performed. PCI did not display a significant improvement in either PFS or OS rates (52-54). In another retrospective study with 1,068 LS-SCLC patients (648 after propensity score matching), PCI was found to significantly reduce brain metastasis rates while not having an effect on OS (55). One-, three-, five-year brain metastasis rates favored PCI compared to non-PCI groups (9.3%, 28.2%, 34.0% versus 27.5%, 38.5%, 40.3%). When one-, three-, five-year OS rates of PCI vs non-PCI groups were compared, this difference was not observed (86.6%, 49.4%, 39.9% vs 85.8%, 49.4%, 34.1%). Median PFS was also found to favor the PCI group (14.7 months vs 10 months) (55). Currently, there are three upcoming clinical trials comparing PCI vs only MRI surveillance in LS-SCLC patients and whose results are yet to be published (41).

In the immunotherapy era, the role of PCI warrants renewed evaluation. ICI may provide systemic disease control, including potential activity against micrometastatic central nervous system disease. In the MRI surveillance era, routine brain imaging enables earlier detection of asymptomatic brain metastases, raising questions about the risk-benefit balance of PCI, particularly regarding neurocognitive toxicity. The optimal integration of PCI, TRT, and immunotherapy remains undefined, and ongoing trials are expected to clarify whether MRI surveillance combined with systemic immunotherapy can safely replace PCI in selected patient populations (51, 52).

The role of PCI treatment in the era of immunotherapy is still not well-established. Ongoing trials such as SWOG 1827 MAVERICK and PRIMALung study, which compare MRI surveillance and PCI, are including patients who underwent immunotherapy; therefore, more clinical data on this matter will be available in due time. Currently, survival analyses of patients who underwent both chemoimmunotherapy and PCI are done with retrospective data. In a retrospective study, one-year intracranial metastasis rates were significantly lowered by ~40% in the PCI cohort, but there was no significant benefit observed for OS and PFS. Subgroup analyses revealed that PCI provided a statistically significant median overall survival advantage of 6.3 months to patients who achieved PR with first-line chemoimmunotherapy. Salvage radiotherapy showed similar survival outcomes to PCI; the only group PCI demonstrated a survival advantage in comparison to salvage radiotherapy was in the subgroup of patients who achieved PR (53).

Second Line Therapy in Small Cell Lung Cancer

Although SCLC is considered to be a chemotherapy-sensitive disease, second-line treatments hold an important role in SCLC treatment, as most patients tend to relapse after achieving complete remission in first-line chemotherapy (27, 56). Patients who show recurrence are categorized as resistant, sensitive, and refractory, depending on when the recurrence occurs (56). Resistant patients relapse less than three months after first-line treatment is over; if patients have a relapse after a longer time, they are considered sensitive, and if they relapse even before the initial treatment is over, they are considered to be refractory (52). Relapsed patients tend to have especially poor prognosis, but sensitive patients harbor the most potential when it comes to responding to second-line therapy (27, 55). Both topotecan and lurbinectedin are approved by the Food and Drug Administration, and are recommended as treatment options by the European Society for Medical Oncology guideline (27). Currently the European Union permits the usage of topotecan for second-line treatment of SCLC, and lurbinectedin is in orphan drug status (27). In different trials, topotecan was found to improve OS in comparison to best supportive care, and produced survival and response rates similar to those of cyclophosphamide, adriamycin, and vincristine (CAV) (57, 58). When compared with topotecan in patients with sensitive relapsed SCLC, carboplatin-etoposide rechallenge resulted in longer PFS (4.7 months vs 2.7 months); however, OS was similar for both treatment arms (59). The ATLANTIS trial compared OS in patients treated with lurbinectin + doxorubicin vs. topotecan or CAV regimens. For both treatment arms, similar OS rates were observed at 12, 18, and 24 months, and the primary endpoint of OS advantage was not met. Treatment-related AEs leading to treatment discontinuation and dose reductions and grade 3 or above hematologic toxicities were seen less in the lurbinectedin/doxorubicin group, in comparison to the control group (60).

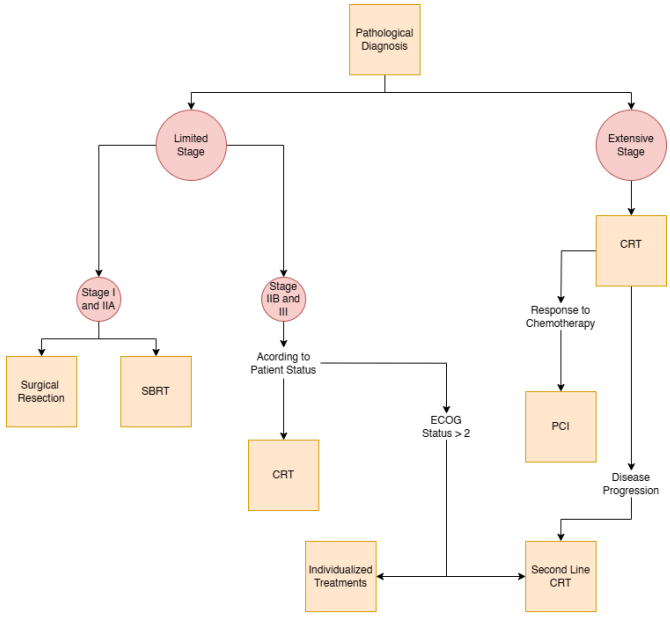

Figure 4: Showing the flowchart of diagnosis and treatment selection process used after the pathological diagnosis with emphasis on immunotherapy integration in first-line treatment for ES-SCLC, consideration of consolidative thoracic radiotherapy, and evolving roles of PCI and MRI surveillance in the immunotherapy era. Radiaiton based treatments such as prophylactic cranial irridation, stereotactic body radiation therapy and definitive concurrent radiation therapy along with surgery and individualized treatments are prefered acording to the patient response and disease progression (59-63).
SCLC: Small cell lung cancer, ES: Extensive-stage PCI: Prophylactic cranial irradiation, MRI: Magnetic resonance imaging, SBRT: Stereotactic body radiation therapy, CRT: Concurrent radiation therapy

Novel Therapeutic Approaches

The tumor immune microenvironment of SCLC is characterized by a highly immunosuppressive phenotype despite the tumor's high mutational burden. SCLC tumors commonly exhibit low major histocompatibility complex class I (MHC-I) expression, limiting effective antigen presentation to cytotoxic T lymphocytes. Additionally, the immune infiltrate is often dominated by immunosuppressive cell populations, including regulatory T-cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages with an M2-like phenotype. This immunological microenvironment contributes to limited immune recognition and represents a major barrier to effective immunotherapy responses (61, 63, 64).

Future therapeutic strategies in SCLC are increasingly focused on rational combination approaches, including immunotherapy combined with radiotherapy, deoxyribonucleic acid (DNA) damage response inhibitors, and epigenetic modulators. Emerging biomarkers such as tumor mutational burden, immune gene expression signatures, and circulating tumor DNA may enable better patient stratification and prediction of immunotherapy benefit (65, 66). In parallel, next-generation immunotherapeutic approaches, including bispecific T-cell engagers and personalized cellular therapies, hold promise for overcoming immune resistance and improving durable disease control (63, 64).

Due to its rapid progress, early-metastatic nature, ability to develop treatment resistance, and few therapeutic targets SCLC remains a hazardous and difficult disease to treat. New approaches in SCLC management are integrating immunotherapy with traditional chemotherapy (CT) and radiotherapy (RT), showing promise in their current situations. Most recently, combining ICI with chemotherapy has become the latest hot topic for SCLC. Different targeted therapies are also becoming more prominent. These novel therapeutic approaches are providing new combinations for SCLC treatment (Figure 5).

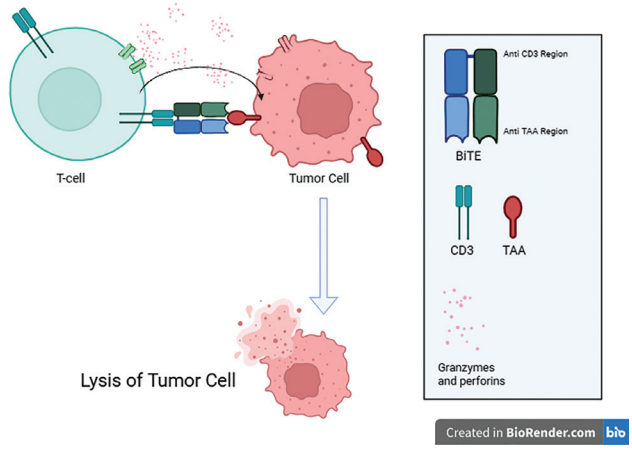

Figure 5: Showing the immuno-specific mechanism seen as a possible future treatment option. With antigen-antibody matchings, the lysis of tumor cells through the use of granzymes and perforins is seen as a mechanism with potential for less agressive and more efficient treatments (65-67).

Anti-Programmed Death-1/Programmed Death Ligand-1

In ES-SCLC patients, combining ICI with etoposide and platinum (EP) CT has proven its efficacy by improving OS and PFS rates. In contrast to CT-only treatments, combining atezolizumab with EP CT as a first-line treatment resulted in a two-month increase (12.3 months vs. 10.3 months) in median OS and almost a month increase (5.2 months vs. 4.3 months) in PFS, according to the IMpower133 trial (NCT02763579) (63, 64). Clinical trials have proved that using anti-programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors like atezolizumab and toripalimab provides notably improved results (64).

Antiangiogenic and Anti-Programmed Death-1

Combining an antiangiogenic (surufatinib) and anti-PD-1 agent (toripalimab) with an EP doublet regimen provided a new route for ES-SCLC treatment. This new regimen achieved tumor shrinkage in all of its patients. Combination therapy of surufatinib and toripalimab resulted in higher anti-tumoral activity whilst reaching clinically acceptable safety (63). Despite these improvements, only a subset of patients derives durable benefit, and resistance to immune checkpoint inhibition remains a major clinical challenge (63).

Bispecific T-cell Engager Molecules

Drugs targeting delta-like-ligand 3 (DLL-3) proteins on tumors are also emerging as a novel therapeutic approach. This new approach allows a T-cell mediated response against tumors. Bispecific T-cell engager molecules simultaneously connect to T-cells and tumor-associated antigens. This engagement provides T-cell activation and proliferation, ultimately leading to tumor shrinkage. Phase 2 clinical trial DeLLphi-301 (NCT05060016) findings show that tarlatamab, a new molecule, achieved significant tumor shrinkages on brain metastases in previously treated patients. In this trial tarlatamab exhibited an objective response rate of 40% in patients with relapsed/refractory SCLC. With long-term responses and adequate safety, tarlatamab is also a promising drug in treating SCLC patients (64, 65).

Poly-Adenosine Diphosphate Ribose Polymerase Inhibitors

Recent studies about poly-adenosine diphosphate ribose polymerase inhibitors (PARPi) have shown that RT with PARPi and anti-PD-L1 can be an effective treatment for SCLC. Olaparib, accompanied by RT, demonstrated cancer cell-specific radio sensitization in SCLC. Subsequently, anti-PD-L1 increases the anti-tumor effect by causing T-cells to infiltrate the tumor. This synergist radiosensitization effect can be utilized as a new combination therapy (66).

Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) are antibodies targeting cancer cells combined with chemotherapeutic agents. ADCs connect to their antigens and enter the cancer cells. After that, their chemotherapeutic agent exhibits its anti-tumoral effect. ADCs targeting delta-like ligand 3 (DLL3s) are still in development. ADCs' potential targets are DLL3, Seizure Related 6 Homolog, CD 276, and Tumor-associated calcium transducer 2. These are targets which are expressed widely in cancer cells (67).

Epigenetic Modulators

Epigenetic modulators aim to reprogram the genetic expression of the tumor cells and make tumor cells susceptible to chemotherapy and immunotherapy. The enhancer of zeste homolog 2 (EZH2) is a functional part of the polycomb repressive complex 2 (PRC2). PRC2, with its histone methyltransferase activity, regulates transcription and is highly expressed in SCLC. EZH2 methylates histones and silences tumor suppressor genes, promoting tumor progression. EZH2 inhibitors aim to suspend this process and improve cellular differentiation. While being early phase and preclinical epigenetic modulators like EZH2 may provide novel combination possibilities against SCLC (68, 69).

Challenges Against Novel Therapeutic Approaches

Even though new therapeutic approaches seem promising, they also have their own challenges. Due to their recent commencement, most of the studies are in early phases and they are conducted with small sample sizes. These studies need more randomized controlled trials in order for us to better understand them.

Resistance to immunotherapy in SCLC can be broadly categorized into mechanisms related to impaired antigen presentation, T-cell dysfunction, and immunosuppressive immune cell infiltration. Loss or downregulation of MHC-I expression reduces tumor antigen visibility, while chronic antigen exposure promotes T-cell exhaustion, characterized by sustained expression of inhibitory receptors such as PD-1. In parallel, the accumulation of immunosuppressive cell populations, including Tregs and MDSCs, further dampens effective anti-tumor immune responses. These mechanisms collectively explain both primary resistance and the development of acquired resistance following an initial response to immune checkpoint inhibition (70, 71).

Resistance is also a challenge in immunotherapy. Many tumors present primary and secondary resistance to ICI. With their unstable genome and heterogeneity, SCLC tumors are highly different genetically and epigenetically. If this genetic alteration is present before treatment and the tumor does not respond to treatment, then primary or adaptive resistance is observed. If a positive response is monitored, however gradually declines, this is reported as a secondary or acquired resistance. Secondary resistance is observed due to the suppression of drug responsive clones and proliferation of drug-resistant clones. Mechanisms of resistance are poorly understood (70).

Another challenge is the toxicity of novel therapeutic approaches. While new agents display promising effects, they also display similar toxicity profiles like their predecessors. Moreover immunotherapy combination therapies have a higher chance of adverse effects. This remains as a limiting factor (71).

Small cell lung cancer is characterized with its lack of predictive biomarkers. This deficiency causes challenges with personalized treatment. Newly studied biomarkers, which are targeted by different immunotherapy agents, make tailored treatment possible. These biomarkers also give information about resistance and side effects of immunotherapy agents (72).

Immunotherapy Resistance Mechanisms

The introduction of ICIs, particularly agents targeting the PD-1 and PD-L1 axis, has represented a significant therapeutic advance in the management of ES-SCLC. However, despite initial enthusiasm and modest improvements in OS when combined with platinum-based chemotherapy, the majority of patients derive limited or transient benefit from immunotherapy, underscoring the presence of both primary and acquired resistance mechanisms (70).

Although ICIs have proved some efficacy in SCLC treatment, a major portion of patients do not respond to treatment or have disease progression after an initial response. This is defined as "immunotherapy resistance" (73). After six months of ICI treatment, if there is disease progression or the best response of the treatment is stable disease this is considered to be primary resistance (74). Acquired resistance is defined as remission of disease after obtaining a objective response or progression after six months of stable disease (73).

Clinical success of ICIs in SCLC is limited compared to NSCLC. Although both cancers are related to high tumor mutation burden caused by tobacco exposure, their response to ICIs and resistance mechanisms have different natures. Also, SCLC differs from NSCLC in the aspect of tumor mutational burden. High tumor mutational burden usually means more T-cell infiltration and neoantigen presentation improving the efficacy of ICIs. In contrast, while having high tumor mutational burden SCLC tumors have immune desert phenotype (failing to cause an immune reaction) causing limited ICI efficacy (75). Tumor mutational burden and ICI response topic is giving us mixed results in SCLC. CheckMate 032 cohort and IMpower 133 cohort have given us mixed results. CheckMate 032 reported an association between high tumor mutational burden and improved outcomes. However, IMpower 133 reported no significant difference (70). These conflicting results indicate that tumor mutational burden alone is insufficient to predict response to ICIs in SCLC. High tumor mutational burden causes increased neoantigen formation and effective anti-tumor immunity requires intact antigen processing and presentation machinery. SCLC causes multiple tumor-intrinsic alterations limiting immune recognition despite this high mutational load.

Reduced MHC-I expression and defects in antigen processing hinder antigen presentation to cytotoxic T lymphocytes causing reduced immune activation. Therefore, high tumor mutational burden does not equal to enhanced T-cell infiltration or immune responses and contribute to primary resistance to ICIs (76). Impairment of the tumor's antigen presentation capacity is one of the fundamental mechanisms underlying resistance to ICIs. Cluster of differentiation 8^+ cytotoxic T-cells need tumoral neoantigens presented on the cell surface via MHC-I molecules. Beta-2-microglobulin, critical in the transport and stability of MHC-I, is indispensable in this process and loss of it can cause the antigen presentation to stop (77). Also decrease in expression of the transporter associated with antigen processing (TAP1/TAP2) proteins which carry peptides to endoplasmic reticulum causes decreased antigen presentation (78). Loss of heterozygosity at the human leukocyte antigen locus during treatment or tumor evolution, causes the tumor to lose its ability to present neoantigens (79).

In parallel, functional exhaustion of tumor-infiltrating T-cells undermines durable immunotherapy responses. Exhausted T-cells in the tumor microenvironment exhibit sustained expression of inhibitory receptors such as PD-1, TIM-3, and LAG-3, along with reduced effector cytokine production and proliferative capacity (70). Importantly, this exhaustion state may not be fully reversible with PD-1/PD-L1 inhibition alone, potentially explaining the modest survival gains observed in pivotal clinical trials (e.g. IMpower133, CheckMate 032) and supporting the exploration of combination strategies targeting multiple checkpoint pathways (77).

Small cell lung cancer subtypes exhibiting higher neuroendocrine phenotype (SCLC-A and SCLC-N) are associated with lower T-cell infiltration and lower MHC-I expression, therefore they are named "immune-cold". These subtypes have an epigenetic shield protecting them from immune recognition. SCLC-I subtype, associated with lower neuroendocrine attributes, has higher antigen presenting capacity and gives a better response to ICIs (77). Neuroendocrine phenotype and immune evasion are closely related to PRC2's subunit EZH2. EZH2 primarily trimethylates the lysine 27 on histone H3 and represses gene expression. EZH2 silences *MHC-I* and *TAP1* genes (70). This mechanism hinders the antigen presenting mechanisms and causes immune evasion. Also, EZH2 represses the expression of T helper 1 chemokines such as CXCL9 and CXCL10 which attract T-cells to the tumor site and causes T-cell exclusion (70).

In addition to tumor-intrinsic mechanisms, immunosuppressive immune cells contribute to immunotherapy resistance. Studies suggest that regulatory T-cells and MDSCs are highly available in SCLC tumors. They interrupt the anti-tumor activity through inhibitory cytokines like transforming growth factor beta, interleukin-10. These cells can limit the immune response and cause poor response to PD-1/PD-L1 blockade (76).

Several resistance mechanisms to immunotherapy have been extensively studied in NSCLC, whereas their relevance in SCLC is only beginning to be clarified. The unique neuroendocrine biology and immunosuppressive tumor microenvironment of SCLC may alter the expression and consequences of these pathways, suggesting that insights derived from NSCLC should be applied cautiously and supported by SCLC-specific evidence.

CONCLUSION

Small cell lung cancer's highly hazardous, malignant, and aggressive nature combined with its mostly limited long-term survival rate makes it a substantial research topic. Contemporary research is promising. New strategies are developed using immunotherapy combinations like combining ICI with chemotherapy or targeted agents. Although these approaches remain largely experimental, they represent important future directions for improving immunotherapy efficacy in SCLC. A better understanding of primary and adaptive resistance mechanisms will be significant to implementing new combinations and improving treatment effectiveness. In this context, immune-related factors such as T-cell exhaustion and immunosuppressive immune cells have gained attention, as they may contribute to reduced immunotherapy efficacy through inhibitory pathways and cytokine signaling. These new strategies are supported by discoveries of new biomarkers and new immunotherapeutic agents. Ongoing and future clinical trials will provide crucial information regarding these strategies and translate them into clinical tools that will improve survival and quality of life in SCLC patients. Integrating evidence with clinical trial data will help optimize treatment algorithms.

Ethics

Ethics Committee Approval: *This study involved a review of the published literature on the current and potential treatment options for small cell lung cancer with also a epidemiological perspective. As this was a secondary analysis of existing data, no new data were collected, and therefore, ethical approval was not required.*

Footnotes

Conflict of Interest: *The authors of this article, Kerem Günel, Nehir Özyedek, and Ahmet Onur Oğuz, are members of the Editorial Board of the Turkish Medical Student Journal. However, they were not involved in any stage of the editorial decision-making process for this manuscript. The editors who evaluated this manuscript are from different institutions.*

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