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Potential evaluation indexes for the efficacy of immunotherapy for in small cell lung cancer

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Abstract: Platinum-based chemotherapy has traditionally been the cornerstone of first-line treatment for small cell lung cancer (SCLC), offering limited but significant survival benefits. In recent years, the advent of immunotherapy has introduced new possibilities for SCLC treatment, particularly through immune checkpoint inhibitors. Despite this progress, the clinical efficacy of immunotherapy remains suboptimal, as reflected in modest response rates and limited durability of responses. These challenges are largely attributed to the low sensitivity and specificity of currently available biomarkers. Consequently, there is an urgent clinical need to identify and validate more reliable biomarkers to guide immunotherapy and optimize patient outcomes. This review critically examines recent advancements in biomarker research within the SCLC landscape, focusing on four key categories: Immune Checkpoint-Related Biomarkers, Tumor-Specific Biomarkers, Tumor Microenvironment-Related Biomarkers, and Peripheral Blood-Related Biomarkers. The overarching goal is to identify biomarker-driven strategies that can refine patient selection, promote personalized and precision-based treatments, enhance quality of life, and ultimately extend survival in SCLC patients.

1. Introduction

Lung cancer is the leading cause of cancer incidence and mortality in China, posing a serious threat to human health. Pathologically, lung cancer can be broadly classified into NSCLC and SCLC. Due to its highly aggressive nature, rapid doubling time, early metastasis, and high recurrence rate, SCLC has the highest malignancy and mortality rates among lung cancer types[1].SCLC is a type of lung cancer with neuroendocrine features, characterized by high tumor mutational burden and immunogenicity, which trigger adaptive immune responses against tumor cells, suggesting that SCLC patients may benefit from immunotherapy[2]. To enhance the effectiveness of immunotherapy, it is crucial to identify effective predictive biomarkers. Established literature indicates that factors such as patient age, smoking status, performance status, nutritional status, histological subtype, and clinical stage are associated with prognosis in SCLC patients. However, these factors are unrelated to treatment approaches and are beyond the scope of this discussion.

2. Immune Checkpoint-Related Biomarkers

2.1 Programmed Cell Death Ligand 1 (PD-L1)

Programmed Death 1 (PD-1) is expressed on effector T cells and interacts with PD-L1 expressed on tumor cells (TC) or within the tumor microenvironment (TME), acting as an inhibitory signal that leads to effector T cell exhaustion. In NSCLC, PD-L1 expression levels have been validated as a predictor of immunotherapy efficacy. The IMpower133 and CASPIAN trials demonstrated that, in extensive-stage small cell lung cancer (ES-SCLC), combining chemotherapy with PD-L1 antibodies as immune checkpoint inhibitors (ICIs) significantly extended median overall survival (mOS) compared to chemotherapy alone[3, 4]. However, in the IMpower-133 trial, PD-L1 immunohistochemical (IHC) analysis was performed on 137 patients, of whom 65 (47.4%) had PD-L1 expression <1% on TC and immune cells (IC). In the atezolizumab group, mOS was significantly improved compared to the placebo group (10.2 months vs. 8.3 months, HR = 0.51, 95% CI: 0.3–0.89). Conversely, no significant improvement in OS was observed in patients with PD-L1 expression ≥1% or ≥5% on tumor or immune cells[5]. Similarly, in the CASPIAN trial, PD-L1 expression was assessable in 54.4% (438/805) of patients, with comparable OS benefits in different PD-L1 subgroups between the durvalumab + EP group and the EP group (HR = 0.61, 95% CI: 0.47–0.79)[4]. These studies failed to confirm PD-L1 as a predictive biomarker for the efficacy of combination therapy with chemotherapy and ICIs. However, subgroup analyses from the KEYNOTE-028 and KEYNOTE-158 trials indicated that patients with high PD-L1 expression derived greater benefits from immunotherapy[6].

The variability in these trial results can be attributed to the broader inclusion of PD-L1 expression in stromal cells in the KEYNOTE studies. Therefore, to improve the accuracy of future research, several measures can be proposed: Firstly, PD-L1 is primarily expressed on immune cells in SCLC[7], and Barzin et al. also found that tumor-associated macrophages (TAMs) express PD-L1. Thus, tumor proportion score (TPS) alone is insufficient to determine PD-L1 expression. Additional metrics such as the immune cell-positive score (IPS) and combined positive score (CPS) should be introduced. Secondly, PD-L1 detection is influenced by spatial and temporal heterogeneity within the tumor. Expression levels are higher in advanced stages and metastases compared to primary tumors[8]. Hence, it is advisable to obtain multiple samples for testing and to perform dynamic monitoring throughout disease progression and treatment. Finally, IHC is the gold standard for PD-L1 expression testing, but there is significant debate regarding the consistency of PD-L1 antibodies and detection platforms. Specific monoclonal antibodies (mAbs) or FDA-approved clones are recommended to improve detection accuracy.

2.2 B7-H3

B7-H3 (CD276) is an important immune checkpoint molecule within the B7 family, playing a dual role in the immune system. As a co-stimulatory/co-inhibitory molecule, B7-H3 both stimulates CD4+ T and CD8+ T cells, promoting cellular immunity, secretion of cytokines like IFN-γ and IL-8, and enhancing the cytotoxicity of CD8+ T cells, while also inhibiting T cells, NK cells, macrophages, and dendritic cells, thereby interfering with regulatory immune processes[9]. IHC analysis of normal tissues showed that B7-H3 is either lowly expressed or undetectable in most tissues, while overexpression was found in up to 65% of human SCLC cases in either cancer cells or tumor-associated immune and stromal cells [10]. In a phase I/II study of the B7-H3-targeting antibody-drug conjugate (ADC) ifinatamab deruxtecan (I-DXd, a topoisomerase I inhibitor), 21 SCLC patients were enrolled, and 11 patients achieved confirmed objective responses (52%; 1 CR, 10 PR), with a median progression-free survival (PFS) of 5.8 months (95% CI: 3.9–8.1) and a

median overall survival (OS) of 9.9 months (5.8–NR)[11]. All evaluable participants exhibited moderate to high levels of B7-H3 expression, suggesting that I-DXd demonstrates strong and durable efficacy in this heavily treated population. However, in another phase I/II trial, the B7-H3-targeting ADC HS-20093 demonstrated partial responses (PR) in 7 out of 9 heavily pretreated SCLC patients (response rate: 77.8%)[12]. Further investigation is needed with larger sample sizes to confirm whether best overall responses or tumor shrinkage are associated with B7-H3 positivity or expression intensity. In addition to ADCs, other immune therapies targeting B7-H3, such as Fc-enhanced monoclonal antibodies, bispecific antibodies, trispecific killer engagers (TriKEs), and CAR-T cells, are under clinical evaluation.

3. Tumor-Specific Biomarkers

3.1 Tumor Mutation Burden (TMB)

TMB refers to the total number of somatic missense mutations, reflecting the tumor's capacity to produce neoantigens. These neoantigens are presented by antigen-presenting cells (APCs) to CD8+ T cells, inducing a cytotoxic T-cell response that leads to the death of neoantigen-dependent tumor cells[13]. The relationship between TMB and response to immune checkpoint inhibitors (ICIs) has been established in several solid tumors, with SCLC being considered one of the tumors with the highest TMB[14]. In the Checkmate 032 trial, TMB was classified into low, medium, and high categories. Patients with high TMB demonstrated longer PFS and OS with nivolumab monotherapy compared to those with low and medium TMB, proving TMB's potential as a biomarker for second-line immunotherapy[15]. However, analysis of the IMpower133 and CASPIAN trials indicated that TMB is not a predictive biomarker for the combination of durvalumab or atezolizumab with chemotherapy[15].

Possible methods to clarify the relationship between TMB expression levels and SCLC prognosis include: Firstly, In NSCLC, different detection methods are known to alter the scope and extent of treatment benefits. Whole-exome sequencing (WES) is the gold standard for measuring tumor TMB, and the use of circulating tumor DNA (ctDNA) from peripheral blood is recommended over tissue samples due to its ability to be repeatedly tested, reflect dynamic changes, cause less trauma, and represent tumor heterogeneity[16]. Secondly, High TMB appears to be a predictor in SCLC patients who have received at least one chemotherapy regimen, but not in treatment-naive patients undergoing immunotherapy, possibly because chemotherapy alters the tumor's immune microenvironment, suggesting that TMB may have stronger predictive value in multi-line treatments[17]. Thirdly, the definition of high TMB can influence the predictive value of immunotherapy, and larger studies are needed to explore the cut-off values for high, medium, and low TMB.

3.2 Molecular Subtypes of SCLC

Based on differences in transcription factor expression and immune pathway activation, four molecular subtypes of SCLC have been defined: SCLC-A (high ASCL1 expression), SCLC-N (high NEUROD1 expression), SCLC-P (high POU2F3 expression), and SCLC-I (high YAP1 and inflammatory gene expression)[18]. Research has shown that neuroendocrine SCLC subtypes (SCLC-A and SCLC-N) exhibit downregulation of several anti-tumor immune-related gene sets, leading to reduced or silenced MHC-I antigen processing and presentation, manifesting as an "immune-cold" phenotype[19]. In contrast, the SCLC-I subtype is characterized by the expression of many immune checkpoints and human leukocyte antigens (HLA)[20]. Tumors of the SCLC-I subtype have higher infiltration of cytotoxic CD8+ T cells, B lymphocytes, macrophages, and NK

cells[21], while HLA class II antigens, primarily expressed on macrophages and lymphocytes, are responsible for antigen uptake, processing, and presentation. A retrospective analysis of transcriptome data from the IMpower-133 trial by Gay et al. found that SCLC-I had greater OS improvement compared to other subtypes[18]. Xie et al.'s retrospective analysis confirmed this finding, showing that patients with the SCLC-I subtype had the greatest OS benefit from immunotherapy[22]. More prospective studies are needed to verify whether SCLC-I subtype patients respond better to immunotherapy.

3.3 Biomarkers Related to Paraneoplastic Syndromes (PNS)

Among patients with PNS, 50% to 80% develop PNS several months to years before the cancer diagnosis[23], and SCLC is the most common malignancy associated with PNS. The clinical manifestations of SCLC-induced PNS mainly involve the endocrine and nervous systems. The endocrine manifestations are caused by ectopic secretion of hormones or peptides by tumor cells, while the neurological manifestations arise due to cross-reactive immune responses against antigens shared by the tumor and normal tissues. DLL3 (Delta-like ligand 3) is highly expressed in neuroendocrine SCLC and is an inhibitory ligand in the Notch signaling pathway. High DLL3 expression is associated with lower neuroendocrine differentiation[24]. Rovalpituzumab tesirine (Rova-T) is an ADC targeting DLL3. In initial clinical trials, patients with high DLL3 expression in tumors exhibited better objective response rates (ORR) (35% vs. 0%) and disease control rates (DCR) (90% vs. 60%) compared to patients with low DLL3 expression; however, these results were not replicated in subsequent phase II and III trials, leaving the predictive value of DLL3 expression as a biomarker uncertain[25].

Regarding tumor-specific genes, transcriptomic characteristics of SCLC can differentiate samples based on antibodies such as anti-GABABR, anti-Hu (ANNA-1), and non-PNS tumors. For instance, compared to anti-Hu and non-PNS SCLC patients, anti-GABABR PNS patients often exhibit gains on chromosome 5q, particularly in the region containing the KCTD16 gene. Research has suggested that this gene region may play a key role in disrupting immune tolerance in anti-GABABR PNS tumors[26]. Future studies may further explore other molecular pathways or individual-specific genes associated with PNS.

4. Tumor Microenvironment-Related Biomarkers

4.1 Inflammatory T Cell Gene Expression Profile (Tcell inf GEP)

The Tcell inf GEP consists of 18 genes that indicate T cell activation within the tumor microenvironment (TME), characterized by active IFN-γ signaling, cytotoxic effector molecules, antigen-presenting and processing machinery (APM), and T cell cytokine activity[27]. In a study by Kanemura et al., immune-related gene expression profiles were analyzed in 135 patients with extensive-stage small cell lung cancer (ES-SCLC) who received chemotherapy or ICIs combined with chemotherapy. The results showed that patients with inflammatory tumors (defined as PD-L1 CPS ≥1% and CD8+ tumor-infiltrating lymphocyte [TIL] density >85/mm²) had a significantly longer mPFS compared to non-inflammatory tumors (10.8 months vs. 5.1 months, p = 0.002, HR: 0.26, 95% CI: 0.09–0.74). In contrast, no significant differences were observed in patients treated with chemotherapy alone[28]. Subsequent studies have further validated these findings. In particular, Xie et al. analyzed gene expression profiles of patients particularly sensitive to durvalumab (D) + tremelimumab (T) + EP, based on samples from the CASPIAN phase III trial. Among patients with the highest 25% APM expression, there was a durable overall survival (OS) benefit (25.9 vs. 10.0 months, HR: 0.26, 95% CI: 0.23–0.84)[22]. It is well-known that the expression of epigenetic

regulators EZH2 and LSD1 is negatively correlated with the efficacy of immunotherapy, suggesting that the epigenetic silencing of APM may be a mechanism of immune evasion in SCLC[29]. These findings suggest that, in clinical practice, Tcell inf GEP can be used to identify patients who may benefit from immunotherapy, enabling personalized treatment.

4.2 Tumor-Infiltrating Lymphocytes (TILs)

TILs directly regulate tumor cell proliferation and metastasis in SCLC through various mechanisms. On the one hand, they secrete cytokines such as IFN-γ, TNF-α, and IL-2, which inhibit tumor growth and promote immune cell activation. On the other hand, TILs regulate the functions of other immune cells, enhancing the overall immune response and forming long-lasting immune memory by activating memory T cells, which improves long-term tumor surveillance[2]. Nearly all mature T cells express CD3+, and a high level of CD3+ TILs is significantly associated with longer survival[30]. CD8+ T cells, also known as cytotoxic T lymphocytes (CTLs), are a subset of CD3+ T cells. Their primary function is to identify and kill tumor cells infected with host cells, playing a key role in cell-mediated immunity. In the CheckMate 032 trial, 286 pre-treatment SCLC tumor samples were analyzed, and CD8+ T cell infiltration was categorized as negative (<1%) or positive (≥1%). The results showed that patients with positive CD8+ T cell infiltration who received nivolumab monotherapy had longer OS (HR = 0.51, 95% CI: 0.27–0.95). A similar trend was observed in patients treated with nivolumab combined with ipilimumab (HR = 0.7, 95% CI: 0.32–1.49)[31]. In addition to retrospective studies, an open-label, single-arm phase II exploratory analysis of recurrent SCLC showed that patients with high levels of baseline CD8+ T cell infiltration experienced tumor regression after treatment with durvalumab and olaparib, indicating that baseline SCLC patients may benefit from immune checkpoint inhibitors. Future large-sample, prospective studies are needed to subtype CD8+ T cell levels within the TME.

5. Peripheral Blood-Related Biomarkers

5.1 Neutrophil-to-Lymphocyte Ratio (NLR)

Neutrophils suppress antitumor immunity by inhibiting T cell proliferation, cytokine secretion, and the cytotoxic activity of T cells and NK cells. Additionally, neutrophils promote genetic instability, tumor cell proliferation, and angiogenesis. Overactivation of neutrophils can lead to tissue damage and tumor progression, enhancing tumor cell invasiveness and metastasis. A reduced lymphocyte count indicates weakened lymphocyte-mediated immune responses[32]. In a study by Riemann et al. involving 40 patients, high NLR was defined as greater than 6.1. Patients in the high NLR group had shorter PFS (12.3 vs. 1 month, P = 0.001) and shorter median OS (14.0 vs. 7.1 months, P = 0.001), indicating that a high NLR before treatment is a prognostic risk factor[33]. Research by Li et al. suggested that dynamic changes in NLR over time are a key nonlinear factor in predicting patient prognosis. Compared to baseline, patients with moderate NLR reduction at 21 days of treatment had the longest OS (27.8 months, 95% CI: 21.8–33.8), while those with significant NLR reduction had an OS of 11.4 months (95% CI: 6.1–16.7)[34]. Further prospective studies are needed to explore the value of NLR as a prognostic biomarker for immunotherapy patients.

5.2 Lung Immune Prognostic Index (LIPI)

Inflammation is evident from the earliest stages of tumor progression. The tumour microenvironment provides biologically active molecules such as growth factors that maintain

proliferative signalling, survival factors that limit cell death, and factors that promote angiogenesis, cancer cell invasion and metastasis [35]. Lactate dehydrogenase (LDH) is a typical marker of inflammation. Mezquita et al. developed the Lung Immune Prognostic Index (LIPI) based on a derived neutrophil-to-lymphocyte ratio [dNLR; neutrophils/(white blood cells – neutrophils)] greater than 3 and LDH levels above the upper limit of normal (ULN). LIPI has been shown to be a potentially useful tool for selecting NSCLC patients for ICI treatment [36]. Zhang et al. conducted a study involving 100 ES-SCLC patients, defining patients with a dNLR ≥4.0 and LDH ≥283 U/L as "poor" (LIPI 2), patients with dNLR <4.0 and LDH <283 U/L as "good" (LIPI 0), and the remaining patients as "intermediate" (LIPI 1). Due to the small sample size, the "poor" and "intermediate" groups were combined for multivariate analysis, which revealed that pretreatment intermediate/poor LIPI (HR: 2.34; 95% CI: 1.13–4.86; P = 0.02) was an independent risk factor for OS. However, pretreatment intermediate/poor LIPI (HR: 1.42; 95% CI: 0.84–2.39; P = 0.19) did not significantly impact PFS[37]. This is the first study to demonstrate that pretreatment LIPI correlates with survival outcomes in SCLC patients treated with first-line ICI. Limitations of this study include the fact that it was a small, single-center, retrospective study with a limited selection of immunizing agents and non-specific LIPI subgroups. Larger prospective studies involving a variety of ICIs are needed to assess the predictive value of LIPI.

6. Conclusion

Immunotherapy has ushered in a new era in the treatment of SCLC, and there is an urgent clinical need to identify appropriate biomarkers to predict responses to immunotherapy. The biomarker data presented in this study are primarily based on retrospective analyses. Therefore, the key challenge moving forward is the need for large-scale prospective studies to validate these findings and confirm their clinical applicability. Additionally, to fully understand the optimal application of immunotherapy in SCLC patients, it is essential to closely monitor the results of clinical trials involving new immunotherapeutic strategies, such as CAR T cells and BiTEs.

Traditional biomarkers like PD-L1 and TMB have demonstrated strong predictive value in NSCLC, yet exploratory analyses in SCLC suggest that patients can derive clinical benefit from immunotherapy regardless of the expression levels of these markers. This has prompted further investigation into combining PD-L1 and TMB as composite biomarkers, potentially offering a more effective strategy for predicting immunotherapy responses in SCLC. PTumor microenvironment-related biomarkers result from the interplay of various factors, and existing studies indicate that they hold promise as predictive biomarkers for immunotherapy in SCLC. eripheral blood-related biomarkers offer advantages such as ease of collection, absence of tissue heterogeneity, and the ability for dynamic monitoring. Consequently, developing predictive models using multiple peripheral blood biomarkers may serve as a promising shortcut to enhance the efficacy of immunotherapy. As research on ICIs and resistance mechanisms continues to evolve, immunotherapy will inevitably be more widely applied in SCLC treatment. Researchers are focusing on exploring new combination therapies, identifying efficient and convenient biomarkers, improving the efficacy of immunotherapy, and expanding the pool of patients who may benefit from these treatments.

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