



Squamous carcinoma of the lung: still a long and winding road to successful treatment



“...as the squamous cell lung cancer treatment landscape evolves many new therapeutic issues have arisen at the same time.”

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Lung cancer is the leading cause of cancer-related death worldwide, accounting for approximately 1.4 million deaths in 2010 in the USA, according to the SEER database [1].

Approximately 85% of newly diagnosed lung tumors are non-small-cell lung cancer (NSCLC) and, among them, 20–30% are squamous cell lung cancer (SQCLC). The incidence of this subtype has now been surpassed by adenocarcinoma, reflecting trends in reduced tobacco exposure with the introduction of filtered and low-tar content cigarettes, as well as changes in cigarette smoke inhalation patterns [2].

The diagnosis of SQCLC is currently performed by light microscopy and relies on the presence of keratinization and/or intracellular bridges. With the increasing need of a correct histological diagnosis in order to choose the right therapeutic regimen, the dichotomy between small-cell lung cancer and NSCLC became obsolete. For such reasons when in poorly differentiated lung carcinomas there is no

clear-cut cellular differentiation at light microscopy, which account for 20–30% of cases, a panel of immunohistochemistry (IHC) markers has been shown to increase the likelihood of an appropriate subtyping. This panel includes at least cytokeratin CK7, CK5, TTF-1 and p63, as demonstrated by a retrospective study performed on fine-needle aspiration cytology cell blocks [3]. Another marker, p40, an antibody that recognizes the Δ Np63-a p63 isoform, is equivalent to p63 in sensitivity but markedly superior to p63 in specificity, which eliminates the potential pitfall of misinterpreting a p63-positive adenocarcinoma or unsuspected lymphoma as a SCC [4].

Current available treatment options for advanced SQCLC rely only on systemic cytotoxic chemotherapy. Patients with a good performance status (Eastern Cooperative Oncology Group performance status 0–1) should receive a platinum agent, cisplatin (preferentially) or carboplatin, plus a third-generation drug (taxanes,

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vinorelbine or gemcitabine). Eastern Cooperative Oncology Group performance status 2 patients are often treated with single-agent chemotherapy, although carboplatin-based doublet could be also considered. Finally, best supportive care (BSC) represents the only option for PS 3–4 patients [5].

Several studies (for review, see [6]) have shown an inferior activity of pemetrexed in combination with cisplatin in SQCLC and this agent is currently not licensed for the treatment of this type of tumor. The histology-related activity of pemetrexed has been related to a different expression of thymidylate synthase (TS), one of the main enzymes of the folate pathway targeted by pemetrexed, with expression being higher in SQCLC and lower in nonsquamous NSCLC [7]. Other markers of chemoresistance such as ERCC1 and BRCA1 equally show higher expression in SQCLC than other histotypes [8].

A large Phase III study that compared carboplatin combined with albumin-bound paclitaxel (nab-PC) or paclitaxel demonstrated a significantly higher ORR with nab-PC than paclitaxel in the overall population (33 vs 25%; $p = 0.005$) and in patients with squamous histology (41 vs 24%; $p < 0.001$), while nab-PC was as effective as paclitaxel in patients with nonsquamous histology (26 vs 25%; $p = 0.808$) [9].

Platinum chemotherapy with poly(ADP-ribose) polymerase (PARP) inhibitors have been studied in clinical trials. Preclinical observations have shown that PARP inhibitors preferentially kill neoplastic cells and induce complete or partial regression in various human tumor xenografts in nude mice treated with platinum agents [10]. However, PARP activity in DNA repair is not fully clear [11], and as a result the biological mechanisms by which PARP inhibitors sensitize cancer cells to platinum chemotherapy remain to be resolved.

Currently the role of targeted therapies in SQCLC remains elusive. Bevacizumab, a monoclonal antibody against VEGF, is an established treatment option combined with chemotherapy in nonsquamous advanced NSCLC only. Such restriction is related to life-threatening or fatal episodes of hemoptysis in bevacizumab-treated patients with SQCLC, as observed in one of the early Phase II trials [12], and the drug is not currently licensed for SQCLC. Several multitargeted, antiangiogenic agents including sorafenib, motesanib and nintedanib have been studied in clinical trials for patients with advanced NSCLC. For most of these agents antitumor

activity has not been seen in SQCLC and occasionally only additive toxicity has been reported (for review see [13]).

Nintedanib, which inhibits VEGF receptor (VEGFR), PDGF receptor (PDGFR) and FGF receptor (FGFR), has been extensively investigated. The LUME-Lung 1 study comparing docetaxel plus nintedanib versus docetaxel plus placebo as second-line treatment in NSCLC patients and in SQCLC showed only a small statistically significant improvement in progression-free survival and no effect on overall survival [14].

SQCLC lacks EGF receptor (*EGFR*) mutations and *ALK* gene fusions, and the occasional detection of these mutations in SQCLC is due to challenges with differential diagnosis with adenosquamous carcinoma and adenocarcinoma, an issue mostly resolved by incorporating IHC markers [15]. Independently from the abovementioned issue, when *EGFR* mutations are detected in SQCLC they are in almost invariably in never smokers.

In a Phase III trial (FLEX) a statistically nonsignificant correlation in SQCLC between increased survival and chemotherapy plus cetuximab, a monoclonal antibody against *EGFR*, was observed in the subgroup of patients with SQCLC [16] and high *EGFR* expression was associated with survival in the study population [17].

When compared with adenocarcinoma, SQCLC is characterized by a more complex genetic profile. Chromosome 3q amplification and chromosome 3p and 9p deletions have been frequently reported. In particular, *SOX2* is amplified in approximately 20% of SQCLC series and, by contrast, *FOXP1* is inactivated in 4% of tumors [18]. The TCGA Cancer Genome Atlas (TCGA) found that the genes significantly mutated include *TP53*, *CDKN2A*, *PTEN*, *PIK3CA*, *KEAP1*, *MLL2*, *HLA-A*, *NFE2L2*, *NOTCH1* and *RBI* [18]. Smokers affected by SQCLC frequently carry *DDR2* and *FGFR2* mutations, while *EGFR*, *MET* and *PIK3CA* mutations are prevalent in never-smokers [19]. Among mutations, the most interesting from a therapeutic point of view are represented by *MDM2*, a negative regulator of p53 [20], *PIK3CA* and *PTEN*, *DDR2*, *FGFR1*, *MLL2* and *ERBB2*.

Constitutive activation of *FGFR1* by gene amplification, translocation or mutation is associated with various malignancies such as breast cancer or myeloproliferative diseases. It has been recently reported that *FGFR1* amplification

occurs in 20% of SQCLC, and preclinical tests have shown that these alterations are therapeutically tractable. These findings make FGFR1 amplification a potential biomarker for lung cancer treatment [21].

The NRF2 pathway, involved in cell response to oxidative stress, and the Eph-ephrin signaling system, especially related to EPHB3 overexpression, have been detected in SQCLC, but the development of effective targeting agents is lacking [22,23].

Several checkpoint receptors expressed on T cells modulate the immune response as part of normal physiological processes to maintain self-tolerance, prevent autoimmunity, suppress inappropriate responses to host antigens and protect nontumor tissues from damage [24]. Tumors can exploit these immune checkpoint pathways to evade the immune response and develop resistance against attack from the immune system. Two such pathways with the potential for therapeutic anticancer targeting include PD-1 and CTLA-4.

Monoclonal antibodies (mAbs) against PD-1 and PDL-1 demonstrated activity in both pretreated and naive patients. In a Phase I trial nivolumab, a fully human mAb directed against the cytotoxic T-cell protein PD1, led to a 23% response rate in previously treated SQCLC patients [25]. In a heavily pretreated group of patients the median OS was 10.1 months, with a 1-year OS of 42% and a 2-year OS of 24% [26]. Another anti-PD1 mAb, pembrolizumab, was tested in a Phase II trial in previously untreated PD-L1-positive NSCLC patients. In the 42 evaluable patients the objective response rate by immune-related response criteria (irRC) was 36% [27]. Two mAbs that target PD-L1, MPDL3280A and MEDI4736, have recently

been tested, reporting comparable results, as reported with nivolumab and pembrolizumab [28,30]. The immunohistochemistry score for PD-L1 expression directly correlated with response rate as smoking status, with 26% of responses in current or former smokers versus 10% in never smokers [29].

In conclusion, as the SQCLC treatment landscape evolves many new therapeutic issues have arisen at the same time. Molecular alterations proven to be predictive tools in oncogene-addicted adenocarcinomas do not apply to SQCLC, probably as a consequence of its more complex genetic profile. However, at the same time the expanding role of next-generation sequencing and its vastly reduced cost paves the way for a more appropriate use of targeted agents, possibly leading to better results even in SQCLC. Moreover, the immunotherapy, with its promising results, has opened exciting new roads that will be thoroughly explored in the near future, both in the advanced and early disease setting. While our knowledge of tumors genetics and microenvironment evolve rapidly, the challenge is to correctly put in the right place each piece of the evolving puzzle to gradually improve patient outcome.

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