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

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 ΔNp63-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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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 anticaner 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 nivolumumab 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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