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Hot Topic

Addressing the unmet need in lung cancer: The potential of immuno-oncology

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ABSTRACT

Chemotherapy is currently the standard of care for non-oncogene-driven advanced non-small cell lung cancer (NSCLC). Due to improvements in chemotherapeutic choices and supportive care, patients currently typically undergo multiple lines of chemotherapy as their disease progresses. Although treatments have improved over recent years, limited benefits are seen, especially in patients receiving later-line chemotherapy, as response rates can be low, response duration short and survival poor. Furthermore, only a small percentage of patients derive benefit from later-line therapy, with most experiencing deteriorating quality of life and significant toxicities. More recently, molecular targeted therapies have provided improvements in outcomes. However, these treatments only offer a clear benefit in subsets of tumours harbouring the appropriate genomic alteration (mutation, amplification, translocation). Most of the genomic abnormalities susceptible to therapeutic intervention are detected in adenocarcinoma, mainly in never smokers, while alterations in the genome of other histological subtypes are known but specific agents targeting these alterations have yet to be developed. Thus, the therapeutic management of these subtypes represents an ongoing challenge. Recent advances in immunotherapy have highlighted the potential of immuno-oncology based treatments for NSCLC, offering the potential to provide durable responses and outcomes regardless of histology or mutation status. This review discusses the current unmet medical needs in NSCLC, the limits of current first-line and later-line chemotherapy and targeted agents, and the emergence of new therapeutic strategies.

Introduction

Most newly diagnosed advanced non-small cell lung cancer (NSCLC) patients present with inoperable (~80%) locally advanced (stage IIIB; 22%) or metastatic (stage IV; 56%) disease [1–5]. In such patients, systemic treatment options are limited, with a median overall survival (OS) of 8–12 months in the clinical trial setting [6]. Because of the high incidence of NSCLC and the unsatisfactory efficacy of systemic treatment, lung cancer is the most frequent cause of cancer death in men, and is likely to be the most frequent cause of cancer death in women in the near future [7,8].

As with many diseases, treatment of NSCLC requires that certain patient groups are considered differently. Elderly patients with NSCLC often present with poor performance status (PS), comorbidities and a higher level of toxicities, especially when exposed to combination chemotherapies [9]. Thus, for a significant proportion of elderly patients, single-agent chemotherapy is still the preferred treatment [6,10–12]. Patients with PS of 2 also require specific treatment consideration and are typically excluded from clinical trials. For these patients, chemotherapy may improve OS and quality of life (QoL) [13], with single-agent chemotherapy a common option; however, carboplatin-based combination chemotherapy should be considered in eligible patients with PS of 2 [6].

World Health Organization (WHO) classification for NSCLC includes many histological subtypes and is broadly categorised as squamous (30%) or non-squamous (70%; including adenocarcinoma, NSCLC not otherwise specified, and other cell types) for therapeutic purposes [14,15]. In routine clinical practice, a panel of immunohistochemistry markers, including at least cytokeratin 7, cytokeratin 5, thyroid transcription factor-1 and p63, has been shown to increase the likelihood of appropriate subtyping [16].

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Advances in our understanding of the molecular biology of NSCLC have led to effective and approved targeted agents for tumours with epidermal growth factor receptor (EGFR) mutations and ALK or ROS1 rearrangements. Additionally, vascular endothelial growth factor (VEGF), heat-shock protein 90 (HSP90), the mammalian target of rapamycin, phosphatidylinositol 3-kinase (PI3 K), BRAF, HER2 and RET translocation have been shown to be additional potential targets of interest [17–20]. *EGFR* mutations are detected in approximately 10% of Caucasian and 30–50% of Asian patients with advanced NSCLC, and are generally more frequent among never-smokers [3,6]. *ALK* gene rearrangements are detected in 2–7% of patients with advanced NSCLC and are more commonly reported histologically in adenocarcinoma and in never-smokers; *ALK* gene rearrangements are often seen in younger patients [3,6].

Targeting oncogenic-driven NSCLC

First-line therapy options

Molecular targeted therapies have improved OS in specific subgroups of NSCLC patients in comparison with historical cohorts [21]. EGFR small molecule tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib and afatinib, and ALK-inhibiting agents such as crizotinib, ceritinib and alectinib, are currently the only truly molecular targeted therapies available for the treatment of advanced NSCLC [22–28]. In randomised controlled trials, these agents have dramatically improved response rate, doubled time to progression, reduced tumour associated symptoms and improved QoL, without improving OS versus chemotherapy. This apparent lack of OS benefit is likely to reflect the confounding effects of crossover between treatment arms in the vast majority of patients in all trials [24,26,28–34]. Furthermore, acquired resistance ultimately develops with all targeted agents.

Squamous cell NSCLC is still treated with cytotoxic chemotherapy alone [3,6]. Squamous cell carcinoma of the lung is closely related to smoking and has a distinct and more complex genetic signature compared with non-squamous tumours, including mutations in TP53, P13KCA, SOX2, fibroblast growth factor receptor (FGFR) and PTEN [14,35,36]. However, there is currently insufficient evidence to suggest that blocking these pathways with targeted agents would represent true therapeutic progress.

Second- and further-line therapy options

Second- or further-line use of targeted agents has also shown efficacy in molecularly selected populations, although with some agents, efficacy may be reduced compared with first-line use [28,34]. Thus, current guidelines recommend TKI and ALK-inhibiting therapy for second- or further-line as well as first-line use in patients with tumours expressing EGFR or ALK mutations [3,6,12].

In contrast to the United States (US) where it is approved for first- and second-line treatment of ALK+ NSCLC, crizotinib was only granted approval in Europe for patients with an *ALK* gene rearrangement who have progressed after platinum-based chemotherapy, following a positive study of second-line crizotinib versus chemotherapy [3,6,28]. However, it is noteworthy that crizotinib was superior to standard first-line pemetrexed plus platinum chemotherapy in a recent trial in patients with previously untreated advanced ALK+ NSCLC, which may lead to an extension of crizotinib's European indication in the future [34]. In April 2014, ceritinib received accelerated approval from the US Food and Drug Administration (FDA) for the treatment of patients with ALK+, metastatic NSCLC and disease progression on, or who showed intolerance to, crizotinib [37]. Alectinib was approved for the treatment of ALK+ NSCLC in Japan in July 2014 [38].

Treating NSCLC without driver oncogenes

First-line therapy options

For patients in whom no driver mutation can be identified, platinum-based doublet chemotherapy remains the mainstay of first-line therapy, although all platinum doublets show relatively similar efficacy profiles. Current ESMO guidelines suggest that 4–6 cycles of chemotherapy should be initiated in patients with favourable PS (PS 0 or 1), while for patients with declining PS of 2, mono-chemotherapy remains an option (gemcitabine, vinorelbine or taxanes); carboplatin-based combination chemotherapy should also be considered in eligible patients [6]. Patients with PS 3–4 should be offered best supportive care (BSC) [6].

Traditionally, the histological subtype of NSCLC did not influence the choice of chemotherapy. However, the treatment landscape has recently changed. Patients with non-squamous NSCLC benefited more (in terms of OS) than squamous patients from cisplatin plus pemetrexed in a large phase III non-inferiority study in patients with stage IIIB or IV NSCLC [39,40]. Hypothesis generating findings support the superior activity of pemetrexed in non-squamous histology due to the differential expression of thymidylate synthase across different histologies [41]. Indeed, clinical benefits of cisplatin plus pemetrexed versus cisplatin plus gemcitabine were more prominent in patients with less than 10% of tumours expressing thymidylate synthase in a recent phase II trial in patients with NSCLC [42].

Although bevacizumab is an established therapy for NSCLC, its role in the treatment paradigm is less straightforward as predictive factors to select patients for efficacy have not yet been established. Two pivotal phase III trials provided the foundation for using bevacizumab in NSCLC [43–45]. Both studies were restricted to non-squamous histology because life threatening or fatal episodes of haemoptysis occurred in patients with squamous histology treated with bevacizumab plus chemotherapy in a phase II randomised clinical study [46].

A growing body of clinical evidence also indicates that maintenance therapy (as continuation or switch therapy) can provide additional long-term benefits, including improved progression-free survival (PFS) and OS [3,6]. Two independent studies have established a definitive role for pemetrexed in switch and continuation maintenance therapy [47,48]. Other agents already approved for second-line NSCLC, such as docetaxel and erlotinib, have also been tested in this setting [25,49]. Furthermore, meta-analyses have consistently demonstrated a benefit, in terms of PFS, for switch and continuation maintenance strategies [50,51], while OS may also be improved without deterioration in QoL [14,52]. The decision of whether to implement maintenance therapy should consider the histology, response to platinum-doublet chemotherapy, residual toxicity after first-line chemotherapy, PS and patient preference [6].

Second-line treatment options

Patients progressing after first-line chemotherapy with PS 0–2 should be offered second-line single-agent chemotherapy, as no benefit has been demonstrated with combination regimens [3,6,53]. Approved treatment choices include docetaxel for all NSCLC histologies [54] or pemetrexed for non-squamous NSCLC [55].

In a phase III study in second- and third-line patients who could not tolerate chemotherapy, erlotinib significantly improved