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Strategies for maintenance therapy in advanced non-small cell lung cancer: Current status, unanswered questions and future directions

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Abstract

Systemic chemotherapy (CT) with platinum-based doublets result in modest improvements in both overall survival (OS) and quality of life in good performance status patients with advanced non-small cell lung cancer (NSCLC). However, although substantial progress has been made in the therapeutic options currently available for these patients, the overall outcome remains poor.

Maintenance therapy for patients who achieved at least stable disease after first-line treatment has been an area of intense investigation in recent years as a way of improving outcomes in metastatic NSCLC. Several alternative strategies for prolongation of initial treatment have been evaluated. These include the prolongation of the initial combination CT regimen until disease progression, unacceptable toxicity or a predefined greater number of cycles, continuation with a lower intensity version of the first-line CT regimen or administration of a new active agent immediately after completion of the first-line therapy (switch-maintenance or early second-line therapy). Treatments that have

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been studied in randomized trials to date include CT, molecularly targeted agents, and immunotherapy approaches. Phase III trials have not revealed a survival benefit for extended first-line CT with combination regimens for more than 4–6 cycles. Nevertheless, early second-line therapy with pemetrexed in nonsquamous tumours and erlotinib have demonstrated to improve OS results, especially in select patient groups characterized by histology and/or molecular profile. This article reviews recent data with maintenance therapy in advanced NSCLC and discusses the implications for routine patient care and future drug development.
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Keywords: Maintenance therapy; Pemetrexed; Erlotinib; Bevacizumab; Epidermal growth factor receptor; Vascular endothelial growth factor receptor; Clinical trial

1. Introduction. What is maintenance therapy?

Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in the industrialized world, responsible for more than a million deaths worldwide each year. Most patients are diagnosed with locally advanced or metastatic disease (≈70–80%), and in this palliative setting balancing efficacy with toxicity is of the utmost importance [1].

The current standard of care for treatment of advanced stage NSCLC patients with a preserved performance status (PS) is a platinum-based regimen, which results in modest prolongation of survival, improvement in cancer-related symptoms and quality of life (QoL) [2–4]. Nevertheless, only approximately 60% of patients will experience disease control at 8 weeks, and the median overall survival (OS) observed in recent studies of platinum-based doublets was 10–13 months, with <5% survival at 5 years [5,6]. Recently, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have emerged as a first-line treatment option for patients whose tumours harbour an activating mutation of the receptor tyrosine kinase [7–10]. Although it is generally accepted that the EGFR inhibitor therapy should be continued indefinitely until disease progression, the optimal duration of first-line chemotherapy (CT) is unclear. Several studies investigating the optimal treatment duration have demonstrated that continuation of combination CT beyond four to six cycles only results in added toxicity without a meaningful improvement in progression-free survival (PFS) or OS, suggesting that the maximum benefit of CT is yielded by the first few cycles [11–15]. So, current guidelines from the American Society of Clinical Oncology (ASCO) [2], the National Comprehensive Cancer Network (NCCN) [16] and the European Society of Medical Oncology (ESMO) [3] all recommend up to a maximum of 6 and minimum of 4 cycles of first-line platinum-based doublet CT for responding patients or those with stable disease (SD). The current practice of adopting a "watch and wait" approach after achieving maximal response provides the opportunity for patients to experience a "drug holiday", but it is often associated with anxiety about disease progression, with particular concern for clinical deterioration and the inability to receive second-line treatment. Before discussing the options, it is worth considering what proportion of patients actually receives second-line therapy. Evidence from recent major clinical trials, such as the Eastern Cooperative Oncology Group (ECOG) 4599 study [17], First-Line Erbitux in Lung Cancer (FLEX) [18] or the trial comparing cisplatin/pemetrexed with cisplatin/gemitabine [19] suggest that this figure is approximately 50–60% of patients treated with front-line therapy.

The addition of molecularly targeted agents such as cetuximab or bevacizumab to first-line combination CT is associated with modest improvement in survival [18–20]. With this approach the targeted agent is usually continued beyond the initial induction phase with the combination therapy. Although this is a biologically rational approach, there is no clinical evidence that patient outcomes are improved with such prolonged treatment. Furthermore, the targeted therapy combinations may be suited for selected subsets of patients with advanced stage NSCLC based on clinical characteristics, anatomy and tumour histology [21].

The relative brief duration of disease control even after a major response to front-line treatment has prompted investigators to pursue other novel strategies to delay progression and improve survival for advanced stage NSCLC [22,23]. Maintenance therapy (MT) is the continued administration of therapy after a specified number of treatment cycles once maximum tumour response or disease stabilization have been achieved. The two treatment strategies to extend the duration of treatment in advanced NSCLC that have been more intensively investigated in last years include "continuation maintenance" and "switch maintenance". Continuation maintenance describes the strategy of continuing a CT or targeted agent that was part of the first-line induction platinum-doublet regimen after a defined number of cycles of combination therapy. If a non-crossresistant agent is used as MT before disease progression after first-line platinum-based CT, this approach can be defined as "switch maintenance", early second-line or sequential therapy.

Although a number of active chemotherapeutic and targeted agents are now available for the treatment of advanced NSCLC, it is clear that not all of them are suited for administration for prolonged number of cycles. The optimal MT agent should be associated with proven efficacy, a favourable toxicity profile and the ability to prolonged administration without significant risk of serious cumulative toxicity. The challenges that lie in interpreting the literature come from the heterogeneity of studies and the lack of consensus with respect to what constitutes MT. This review summarizes the rationale, current data and perspectives of maintenance and early-second line treatment in patients with advanced NSCLC.

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