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REVIEW ARTICLE

Controversies in the management of advanced non-small cell lung cancer: maintenance therapy

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Summary

The majority of patients with non-small cell lung (NSCLC) present with advanced, metastatic disease at the time of diagnosis. The current state of the art for the management of this condition is first- and second-line chemotherapy (CT), along with appropriate supporting care measures, which are supposed to alleviate symptoms and to improve survival. During the last years, maintenance therapy (MT) was included in the therapeutic algorithm for these patients. MT could be defined as continuation of an active treatment until disease progression in patients who demonstrated a non-progressing status following induction chemotherapy. Despite the results of several randomized trials showing a significant benefit by using this approach, the strategy is far from being universally accepted. The internationally recognized guidelines provide different recommendation when it comes to this topic, while some major drawbacks in the design of the positive clinical trials may have distorted the relevance of the communicated data. This paper aimed to review the most contentious aspects which should be considered while contemplating the use of MT in the daily clinical practice.

Key words: controversies, maintenance therapy, non-small cell lung cancer

Introduction

MT in NSCLC may be defined as continuation of an active treatment until disease progression (PD) in patients who have demonstrated at least a non-progressing status following the first-line CT. First-line CT is limited to 4 cycles. Continuation and switch maintenance are the two major strategies included in this concept. Some recently published review papers are considering MT as a step forward in the general management of NSCLC [1]. However, we need to be vigilant with respect to the clinical implications of this new strategy, as lots of controversial issues are still surrounding this new concept. Further on, in this paper, we are going to pass through some contentious areas which should be kept in mind when implementing MT in our daily clinical practice.

Which is the status of MT in the international guidelines?

Searching the guidelines for answering this basic question looks similar as walking on quick sands. The ASCO (2009) guideline definitely does not recommend MT [2]. The ESMO (2010) guideline leaves us without a clear recommendation: "the role of maintenance treatments is not definitively established; treatment decisions have to be made on an individual basis; superiority of immediate maintenance therapy versus delayed therapy is not proven" [3]. The NCCN (2011) guideline recommends various maintenance agents and strategies marking them as being more or less consistent in this setting (from category 3 up to category 1) [4]. One may conclude that consulting the guidelines drives us more confused.

Which is the approval authorities signal on this issue?

For continuation maintenance of monoclonal antibodies used concurrently with CT in first-line, the status is similar as confirmed for their first-line use (approved for bevacizumab but not approved for cetuximab). Peme-

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trexed was approved for switch MT in non-squamous histology by both EMEA and FDA. Erlotinib followed a more distorted pathway for the same indication. The FDA Oncologic Drugs Advisory Committee voted 12-to-1 against the approval, due to the modest benefit on overall survival (OS) in the SATURN trial (12 vs. 11 months) [5]. Unexpectedly, FDA has approved an expanded indication for erlotinib in patients whose the disease has not progressed after 4 cycles of platinum-based CT. Moreover, the FDA approval covers the indication of maintenance erlotinib for patients who previously responded to the first-line CT, for whom the benefit is virtually absent (HR=0.94, p=0.61) [6]. More refined, EMEA took into account the previous information and approved erlotinib for MT only for patients with stable disease (SD) after 4 CT cycles. One may conclude that after reviewing the approval authorities signal we are still confused.

Which are the major drawbacks in the design of the MT studies?

Continuation maintenance with bevacizumab and cetuximab, after being used concurrently with the first-line CT, was a built in strategy in 2 positive randomized trials [7,8]. We have no clear message whether the benefit was derived from the MT or a better first-line approach [9,10].

The *switch maintenance* trials included 4 cycles of induction CT as a patient selection strategy. Only the non-progressing subjects were randomized for MT or follow up. The number of cycles included in the induction phase is based on the results of some trials evaluating the optimal duration of first-line CT in stage IV NSCLC [11,12]. These trials randomized patients either to 3-4 initial CT cycles or a longer CT duration. OS survival and response rates were similar between short duration and long duration groups. Nevertheless, neither trial addressed the more specific question of whether patients who are responding to CT, and tolerating CT well, benefit from treatment beyond 3-4 cycles. As such, we may doubt about the optimal duration of induction therapy in responding patients for whom 6 cycles might be more appropriate, as recommended by the actual guidelines [2,3]. Some supporting data of this assumption are emerging from the IFCT-GFPC 0502 study. Eight hundred and thirty-four patients with stage IIIB/IV NSCLC were started on cisplatin/gemcitabine, and then those who had not progressed after the first 4 cycles were randomized to either observation, continuous maintenance with gemcitabine, or switch maintenance with erlotinib [13]. The best results in terms of improved progression-free survival (PFS) were recorded in the gemcitabine continuation arm (HR=0.55, <0.0001), while for the erlotinib switch maintenance arm the benefit was less (HR=0.82, p=0.002). Moreover, the greatest benefit with gemcitabine maintenance was observed in patients with *an objective response* to first-line therapy as opposed to subjects with SD (HR: 0.44 vs. 0.68), which suggests that the full benefits of first-line therapy have not necessarily been achieved after 4 CT cycles only.

Another criticism of the switch maintenance trials is the insufficient crossover of patients in the non-interventional arm to subsequent therapy. In the JMEN and SATURN trials less than 20% of the patients in the placebo arms received pemetrexed or a tyrosine kinase inhibitor (TKI) respectively, following disease progression [5,14]. This bias seems to be reinforced by the IFCT-GFPC study, which mandates pemetrexed administration in all 3 arms after disease progression. Despite being positive for PFS, no benefit in OS survival for any maintenance arm was observed [13]. Another important observation on this issue came out from the Fidias's study, which randomized non-progressing patients after induction CT for immediate vs. delayed docetaxel [15]. OS of patients in the delayed arm who actually received docetaxel therapy (62% of 156) was 12.5 months (which was identical to the OS observed in the immediate docetaxel arm (12.5 months). These data underscore the controversy of timing vs. access to second-line therapy. One may conclude that substantial drawbacks in the design of the maintenance trials could be identified, and some of them may have distorted the relevance of the data.

Which patients, which agent?

From the clinician's point of view this is the most important question but nevertheless extremely challenging. Firstly, it must be stressed that MT is not suitable for all patient population. Two major conditions make a patient eligible for this strategy: a non-progressing status after 4 CT cycles and an ECOG performance status (PS) 0-1. This accounts for approximately 50% of the whole patient population [5,13,15]. Patients with an altered PS may not benefit from MT, despite having no tumor progression [16]. The tumor biological behavior, reflected by the initial response to CT, seems to impact on the MT benefit. For instance, maintenance erlotinib is more effective in patients who have stable disease (SD) after first-line CT as opposed to responding patients who virtually derive no benefit [6]. In contrast, continuation maintenance with gemcitabine is more effective in patients who have an initial response as compared with patients with SD [13].

Histology and the tumor genetic profile are to be considered when choosing the agent for MT. Pemetrexed and bevacizumab should be used exclusively in patients with non-squamous histology. Docetaxel may be used regardless of the histological type but excessive toxicity may be of concern. Despite being clinical relevant (12.3 vs. 9.7 months), the data on the OS benefit for docetaxel are statistically not significant [15]. On the other hand, the benefit in OS with erlotinib is statistically significant but clinically modest (12.3 vs. 11.1 months) [5]. The most impressive PFS benefit was noted in patients with EGFR mutations (44.6 vs. 13.0 months). This accounts for approximately 3% of the initial population. Paradoxically, the OS improvement was less in this category (HR=0.83) compared with the patients with wild type EGFR (HR=0.77) [17].

Concluding remarks

Despite the fact that many conflicting data have been underlined, I would like to conclude with a clearer message. We are facing the painful birth of a new concept in the management of advanced NSCLC. Some data are contradictory, some others are more relevant. Many controversies are already here, some others are still to come. For now, MT should be reserved for a *selected category of patients* and should not be applied as a one-size-fits-all approach. Clearly, we need more informative data regarding patient selection and choice of therapy. The additional toxicity inevitably associated with the MT should be balanced against the expected clinical benefit, keeping in mind the clinical profile of the patient. In daily practice we currently see elderly patients, with associated comorbidities and residual toxicity after first-line CT. For some of those, who successfully went through the stressful first-line CT, a treatment holiday within a rigorous follow up program, associated with a more consistent medical involvement in the palliative care may still stand as the best alternative [3,18].

Conflict of interest

Mircea Dediu served as a consultant and advisory board member for Sanofi-Aventis, Eli Lilly and Roche. His contribution was financially compensated.

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