Review

Maintenance Therapy for NSCLC: Consensus and Controversy

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ABSTRACT

Nowadays, advanced non-small cell lung cancer (NSCLC) is still an incurable disease. However, recent researches on maintenance therapy have led to considerable progress. Recently, pemetrexed and erlotinib have been approved for maintenance chemotherapy by both the U.S. Food and Drug Administration and European Medicines Agency. However, there are not adequate data to support the maintenance therapy as the standard treatment for advanced NSCLC and there has been no conclusive predictor of who will get benefit from maintenance chemotherapy and what type of maintenance, continuation or switch, is preferred. This article reviews the main studies on maintenance therapy of advanced NSCLC and discusses the results available to date.

Key words: Non-small cell lung cancer; Maintenance therapy; Pemetrexed; Erlotinib

Introduction

Non-small cell lung cancer (NSCLC), including squamous carcinoma, adenocarcinoma and large cell carcinoma, accounts for about 85% of all lung cancer types with approximately 65%–70% of patients presenting with advanced disease at the time of diagnosis[1]. The current practice of first-line therapy for advanced NSCLC is four to six cycles of platinum-based combination chemotherapy followed by treatment break in non-progressive status[2]. Therefore, after 4-6 cycles of treatment, non-progressing patients enter in the so called "watch and wait" period in which they perform periodical disease restaging until the progression is reported then a second-line treatment is started. Nevertheless, only approximately 60% of patients will experience disease control at 8 weeks with platinum-based therapy[3], and the median overall survival (OS) observed in recent trials of platinum-based double-agent chemotherapy was 10 to 13 months[4, 5]. For improving survival outcomes of patients with NSCLC, a prolonged treatment through the "watch and wait" period was investigated. This further treatment is called as maintenance therapy, which consists either of drugs included in the induction regimen (continuation maintenance) or other non-cross-resistant agents (switch maintenance). Recently, the results coming from randomized trials are promising. Here, we report them and discuss the consensus and controversy in this new setting.

Continuation Maintenance with Cytotoxic Agents

Pemetrexed

Pemetrexed is an anti-metabolite that inhibits at least three enzymes involved in the folate pathway including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT). Because of the differential expression of TS, non-squamous patients are more reliable to respond to pemetrexed-based therapy than those with squamous cell carcinoma[6, 7]. PARAMOUNT, a major phase III study of continuation maintenance was released in the 2011 American Society of Clinical Oncology (ASCO) annual meeting. In this trial, patients with wet stage IIIB/IV non-squamous NSCLC were initially treated with cisplatin and pemetrexed every 3 weeks for 4 cycles. Subsequently, patients with complete response/partial response or stable disease (CR/PR or SD) were randomized 2:1 to receive maintenance pemetrexed every 3 weeks with best supportive care (BSC) or BSC alone until disease progression or unacceptable toxicity. The primary endpoint was progression free survival (PFS). Following 4 cycles of cisplatin and pemetrexed, 539 non-progressive patients were randomized to receive pemetrexed+BSC (n=359) or placebo+BSC (n=180). The median PFS was 4.1 months for pemetrexed arm and 2.8 months for control arm. The differences in PFS between the two arms were statistically significant [hazard ratio (HR)=0.62]; [95% confidence interval (95% CI): 0.49–0.79], P=0.00006). Maintenance therapy was well tolerated, and the quality of life evaluation (EQ-5D) showed there was no significant difference between two arms.

Gemcitabine

Up to date, there were three large phase III studies of gemcitabine continuation maintenance[8-10], which enrolled 1,705 patients. In the trial by Brodowicz, et al., patients

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received initial therapy with cisplatin and gemcitabine for four cycles. If the patients who did not experience disease progression, then they were randomized to single-agent gemcitabine or observation. The primary objective was time to progression (TTP). Of the 352 patients enrolled, 206 (59%) were randomized to gemcitabine (n=138) or BSC (n=68). Patients in the gemcitabine arm compared with the BSC experience statistically significant longer TTP (3.6 months vs. 2.0 months, $P<0.001$), but there is no significant difference in OS (10.2 months vs. 8.1 months, $P=0.172$). A subset analysis of good and poor performance status (PS) patients was performed for OS from time of randomization, which showed patients with good PS got benefit in OS from maintenance therapy (22.9 months vs. 8.3 months) and those with poor PS could not (7.0 months vs. 7.7 months). In the 2010 ASCO annual meeting, Belani, et al. presented the results of a phase III trial evaluating the efficacy of gemcitabine as maintenance therapy. Following 4 cycles of carboplatin and gemcitabine, 255 non-progressive patients were randomized to receive gemcitabine+BSC (n=128) or BSC alone (n=127). The median PFS was 3.9 months for gemcitabine and 3.8 months for BSC arms. Median survival time (MST) was 8.0 months for gemcitabine and 9.3 months for BSC. The differences in MST between the two arms were not statistically significant (HR=0.97, 95% CI: 0.72–1.30, $P=0.84$). It was a negative study, but the factors that nearly two thirds of patients had a PS of two and less than 20% of patients received post-study treatment maybe influenced the results partly. The third study was presented by Perol, et al. in 2010. After four cycles of cisplatin+gemcitabine, the patients without disease progression were randomized to observation (n=155), or to receive either gemcitabine (n=154) or erlotinib (n=155) as maintenance therapy until disease progression. Median PFS was 1.9 months in the observation arm, 3.8 months in the gemcitabine arm, and 2.9 months in the erlotinib arm, respectively. The difference of PFS between the observation arm and gemcitabine arm ($P<0.0001$) or erlotinib arm ($P=0.002$) was significant. OS data were immature and final results are awaited.

Paclitaxel

Belani, et al. conducted a phase III trial[11], which enrolled 401 untreated advanced NSCLC. After initial chemotherapy with carboplatin and paclitaxel, those with no disease progression were randomly assigned to either weekly paclitaxel (n=65) or observation (n=65). Median TTP and MST were 38 and 75 weeks in the paclitaxel arm, 29 and 60 weeks in the observation arm, respectively. There was no significant survival difference between two arms. This trial was designed to assess the feasibility of paclitaxel maintenance, so the number of enrolled patients was not adequate to support any conclusions on the efficacy of this setting.

Continuation Maintenance with Targeted Agents

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody (Ab) that binds to and neutralizes human vascular endothelial growth factor (VEGF). Two randomized phase III trials[12, 13] resulted in improved response rates (RR) and PFS when bevacizumab was added to a combination chemotherapy regimen with carboplatin/ paclitaxel and cisplatin/gemcitabine, respectively in chemotherapy-naive advanced NSCLC patients with nonsquamous histology, and bevacizumab was administered as maintenance treatment until disease progression or intolerable toxicity in both studies. Prolongation of OS has only been demonstrated for the carboplatin/paclitaxel/ bevacizumab combination in ECOG 4599 trial (OS: 12.3 months vs. 10.3 months; HR=0.80; $P=0.003$), but not for cisplatin/ gemcitabine/bevacizumab combination in AVAIL study ($P=0.761$). Nowadays, there are no conclusive data on the necessity of maintenance bevacizumab. Interesting preclinical observations suggest that taxanes induce proangiogenic bone marrow derived circulating endothelial cell mobilization relevant for tumor re-growth after chemotherapy[14]. Its prevention by VEGFR blocking Abs may be the reason why the anti-tumor effects is amplified compared to the gemcitabine combination. Further investigations are needed also in this field.

Cetuximab

Cetuximab is an inhibitory anti-EGFR Ab which interacts with domain III of the soluble extracellular region of EGFR, preventing the receptor from adopting the extended conformation required for dimerization. Pirker, et al. conducted a phase III trial in which patients with EGFR-expressing wet IIIB or IV NSCLC were randomized either to chemotherapy with cisplatin and vinorelbine alone (n=568) or cisplatin and vinorelbine plus cetuximab (n=557)[15]. In the cetuximab arm, cetuximab was administered concurrently with chemotherapy and was continued after the end of chemotherapy until PD or unacceptable toxicity. Median PFS was 4.8 months in each arm; however, OS was significantly improved in the cetuximab arm (median 11.3 months vs. 10.1 months, HR=0.871, 95% CI: 0.762–0.996, $P=0.044$). Notably, the benefit of cetuximab was seen irrespective of the histological sub-type, which would make the drug particularly attractive for patients with squamous cell carcinoma where treatment options remain limited. The main controversy of this study included the relatively small survival benefit of less than 2 months, the lack of benefit on PFS and the patient selection based on a "weak" biomarker (EGFR protein expression). In 2011, O'Byrne KJ, et al.[16] performed a retrospective analysis of data from the FLEX study, which investigated whether candidate biomarkers (KRAS mutations, EGFR mutations, EGFR copy number and PTEN expression) were predictive for the efficacy of chemotherapy plus cetuximab in this setting. Unfortunately, comparisons of treatment outcome between the two groups (chemotherapy plus cetuximab vs. chemotherapy alone) indicated that these biomarkers were not of predictive value. In the same time, Gatzemeier U, et al.[17] found that first-cycle rash was associated with a better outcome in patients with advanced NSCLC who received cisplatin and vinorelbine plus cetuximab as a first-line treatment. In the other study[18], in which cetuximab was combined with carboplatin and paclitaxel, in contrast, no survival advantages were demonstrated.