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.

Switch Maintenance with Cytotoxic Agents

Pemetrexed

A randomized, double-blind, phase III trial (JMEN study)[19] compared the efficacy and safety of pemetrexed vs. placebo in patients who had not progressed after 4 cycles of platinum-based induction chemotherapy. The initial therapy did not contain pemetrexed. Patients were randomized (2:1 ratio) to either pemetrexed (500 mg/m^2, day 1) plus BSC, or intravenous placebo plus BSC in 21-day cycles until disease progression. PFS was chosen as the primary endpoint. A total of 663 patients (441 in the pemetrexed arm and 222 in the placebo group) were randomized. Median PFS was 4.3 months in the pemetrexed arm and 2.6 months in the placebo arm (P<0.0001). OS was also significantly favored in the pemetrexed arm (13.4 months vs. 10.6 months, P=0.012). Subgroup analysis revealed that the survival benefit of maintenance pemetrexed was seen in patients with non-squamous histology but not in patients with squamous histology. MST was 15.5 months in the pemetrexed arm and 10.3 months in the placebo arm for non-squamous histology (P<0.0001), whereas 9.9 months in the pemetrexed arm and 10.8 months in the placebo arm for squamous histology (P=0.678). Pemetrexed toxicities were generally mild, and no treatment-related deaths were observed. This trial led the approval of maintenance pemetrexed in Europe and the United States for patients with nonsquamous NSCLC who have completed four cycles of platinum-based double-agent chemotherapy.

Vinorelbine

The trial by Westeel, et al.[20] investigated single-agent vinorelbine or BSC. Those with stage IIIB disease received two cycles of (mitomycin-ifosfamide-cisplatin) MIC followed by thoracic radiation, and those with wet IIIB and IV disease received four cycles of MIC. A total of 573 patients were registered, and 227 responded to induction treatment, and 181 (32%) were randomly assigned to weekly vinorelbine (n=91) and observation (n=90). One and 2 year survival rates were 42.2% and 20.1% in the vinorelbine arm and 50.6% and 20.2% in the observation arm, respectively (P=0.48). There was also no difference between the two arms in PFS (P=0.32). The main toxicity was hematologic.

Docetaxel

A phase III trial by Fidias, et al.[21] investigated immediate compared with delayed docetaxel, an established second-line agent, in patients who had stable or responding disease after four cycles of carboplatin and gemcitabine. After four cycles of initial chemotherapy, 309 of 566 patients with no disease progression were randomized to either immediate or delayed docetaxel. Median PFS was significantly better in the immediate arm than the delayed arm (5.7 months vs. 2.7 months, P=0.0001). OS was also better in the immediate arm. However, the difference was not significant (12.3 months vs. 9.7 months, P=0.0853). The toxicity associated with immediate and delayed docetaxel was similar.

Switch Maintenance with Targeted Agents

Erlotinib

Erlotinib is a small molecule tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR) given orally daily. In the previous studies, concurrent administration of erlotinib with chemotherapy was not superior to chemotherapy alone. Recently, two randomized phase III trials investigated the role of erlotinib as maintenance therapy. Sequential Tarceva in Unresectable NSCLC (SATURN) is a randomized, placebo-controlled phase III trial comparing maintenance erlotinib with a placebo, which enrolled 889 patients with no evidence of disease progression after four cycles of platinum-based chemotherapy[22]. The primary endpoint was PFS in all patients. They were randomized to receive either oral erlotinib 150 mg/day (n=438) or placebo (n=451) until progression or unacceptable toxicity. The primary endpoint was PFS in all patients. Both PFS and OS were significantly better in the erlotinib arm (12.3 weeks vs. 11.1 weeks, HR=0.71, 95% CI: 0.62–0.82, P<0.0001 for PFS; 12.0 months vs. 11.0 months, HR=0.81, 95%CI: 0.70–0.95, P=0.0088 for OS). The second phase III trial (ATLAS) was based on these data through the combination of erlotinib and bevacizumab studied as maintenance treatment[23]. This study involved 743 patients with advanced NSCLC who were treated with four cycles of chemotherapy (platinum-containing doublets) and bevacizumab. Patients who did not progress were randomized to maintenance therapy with bevacizumab alone or bevacizumab plus erlotinib until progression. The main primary was PFS. The results showed a significant increase in median PFS from 3.71 months for bevacizumab alone to 4.76 months for bevacizumab plus erlotinib (HR=0.71, 95%CI: 0.58–0.86; P=0.0006). No difference was reported in terms of OS, secondary endpoint of the trial, between the two arms with 15.9 months for the combination arm vs. 13.9 months for bevacizumab alone group (HR=0.90, 95% CI: 0.74–1.09, P=0.2686). However, the difference of two months in OS is also promising. As a result of these two trials, erlotinib was authorized in Europe and the United States as maintenance therapy.

Gefitinib

In 2010, Takeda, et al. reported a phase III trial (WJTOG0203)[24], which explored the efficacy of gefitinib as maintenance therapy in Japanese patients. The untreated patients with stage IIIB/IV NSCLC were randomly assigned to either platinum-doublet chemotherapy for up to six cycles (arm A, n=301) or platinum-doublet chemotherapy for three cycles followed by gefitinib until disease progression (arm B, n=302). Median PFS was 4.3 months for arm A and 4.6 months for arm B (P<0.001), but OS was almost identical between the two arms (12.9 months for arm A, 13.7 months for arm B, P=0.11). Gaafar, et al. conducted a phase III trial in Europe[25], in which patients with advanced NSCLC not progressing after four cycles of platinum-based chemotherapy were randomized to receive either gefitinib (n=86) or placebo (n=87) until progression. PFS was significantly better in the gefitinib arm (4.1 and 2.9 months, P=0.0015), but OS

was not statistically different (10.9 and 9.4 months, *P*=0.2). In the 2011 ASCO annual meeting, Zhang, et al. presented a phase III trial (known as the INFORM) investigated the maintenance therapy for gefitinib compared with placebo after four cycles initial platinum-based combination chemotherapy, and the primary endpoint was PFS. Of the all patients enrolled, 296 patients did not experience disease progression and were randomized (1:1 ratio) to gefitinib (n=148) and placebo (n=148). Patients in the gefitinib arm compared with placebo arm experienced an improvement in PFS (4.8 months vs. 2.6months, *P*<0.0001), but no statistically significant improvement in OS (18.7 months vs. 16.9 months, *P*=0.2608). In the sub-analysis of patients with EGFR mutations, the PFS in gefitinib arm was significantly better than that in placebo arm (16.6 months vs. 2.7 months, *P*<0.0001).

Controversy on Maintenance Therapy

Role as standard setting of maintenance therapy

Are there adequate data to support the maintenance therapy as the standard treatment for advanced NSCLC? Although, pemetrexed and erlotinib were approved in Europe and the United States as maintenance therapy, the role of this new setting still remains controversial. The patients eligible for the maintenance trials were patients who are able to tolerate chemotherapy and whose disease had demonstrated SD or PR. However, Patients randomized to the placebo arm received second-line therapy at a lower rate. In the JMEN study, only 18% of patients received pemetrexed as post-study treatment in the placebo arm. So this study only showed that pemetrexed can significantly improve the survival of patients who receive the agent. Similarly, the SATURN study showed only 21% of patients randomized in the placebo arm received at progression erlotinib as standard second-line therapy. So we could not draw a conclusion that pemetrexed or erlotinib as maintenance therapy is superior to those as second-line therapy or third-line therapy.

Optimal candidate of maintenance therapy

Who may get benefit from maintenance chemotherapy? Which is the better choice between continuation maintenance and switch maintenance? The primary goal of therapy for advanced NSCLC is palliative. Although the rate of severe toxicities observed with maintenance therapy has been low, a prolonged exposure to grade 1 and grade 2 toxicities may adversely impact patients' quality of life. We consider that the eligible patients should have a PS of 0 or 1 and wish to continue treatment. However, Sun, et al. performed a retrospective analysis, according to which, patients with poor PS could also get benefit from maintenance therapy. The authors explained those patients with poor PS were less likely to receive second-line chemotherapy[26]. To date, EGFR mutations are considered the most important predictive molecular factor for NSCLC receiving TKIs therapy, and which are detected mainly in Asians, females, adeno-carcinomas, and never-smokers. In the sub-analysis study (SATURN and INFORM), the patients with EGFR gene mutation derived greater survival improvement than those with EGFR wild type. So whether the EGFR mutation testing is necessary for the patients, who wish to receive EGFR-TKI as maintenance therapy.

Zhang, et al. performed a meta-analysis, which investigated maintenance therapy with either a continuous or a switch strategy for advanced NSCLC. The trial included 3,736 patients and showed the difference in OS between the two maintenance strategies was not statistically significant (*P*=0.777)[27]. According to the previous studies, the patients whose response to induction chemotherapy was SD may benefit more from switch maintenance than patients who achieve PR or CR. Conversely, it seems that patients who achieved PR or CR may derive more benefit from continuation maintenance than those who have SD after induction chemotherapy.

Budget impact of maintenance therapy

Carlson, et al. assessed the budget impact of adding erlotinib for maintenance therapy in the United States. This study found that the overall budget impact of erlotinib as the maintenance setting was relatively small because of low cost of side-effects[28]. Klein, et al. conducted a study of the cost-effectiveness of pemetrexed as maintenance therapy compared with observation, which revealed that the incremental cost per life-year gained was $122,371[29]. The issue of selection of patients who benefit from maintenance therapy is interrelated with economic costs of maintenance therapy. Further research may be warranted to estimate the economic impacts of erlotinib or pemetrexed as maintenance therapy vs. alternative treatments in Chinese patients.

Maintenance therapy for Asian NSCLC

Of the all 663 patients, 129 East Asian patients (28.6%) enrolled the JMEN study. The OS was not significantly different in the East Asian patients (19.7 months for pemetrexed arm, 16.4 months for placebo arm; *P*=0.6701). However, the OS was significantly different in non-East Asian patients (13.2 months for pemetrexed arm, 8.5 months for placebo arm; *P*=0.0005). Similarly, the SATURN study included 125 Asian patients (14%) of the all 889 patients. The OS was also not significantly different in the Asian patients (*P*=0.0931), and but the difference of OS in whole patients was significant (*P*=0.0088). In Asian subgroup, there is tendency not to show survival benefit with maintenance therapy, the reason of which is unclear.

Summary

A new strategy is rising in the treatment of advanced NSCLC replacing the "watch and wait" policy. However, to date there is still a lack of trials comparing the strategy of maintenance therapy to classical second-line treatment. This new setting needs to be refined in the next few years performing further studies to clarify its role as standard treatment. Simultaneously, the new anti-cancer drugs as maintenance therapy seem to warrant further investigation.

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