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ORIGINAL ARTICLE

Shifting the Paradigm for Maintenance Therapy for Non–small-cell Lung Cancer

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ABSTRACT

Systemic chemotherapy has been the standard treatment for advanced / metastatic non–small-cell lung cancer, particularly in those who do not harbour an epidermal growth factor receptor mutation. In the last decade, there was no established evidence to justify the use of more than 4 to 6 cycles of chemotherapy. However, the use of maintenance systemic chemotherapy and more recently targeted therapy for those who do not show evidence of benefit after standard chemotherapy have been demonstrated to delay progression and more importantly prolong survival. Use of pemetrexed after standard non-pemetrexed chemotherapy has brought an improvement in median survival by 2.8 months. The use of more easily administered erlotinib as maintenance therapy after chemotherapy has been shown to improve the median survival by 1.0 month. Use of bevacizumab, an anti-vascular endothelial growth factor receptor monoclonal antibody, combined with standard chemotherapy to start with also appears to be safe and efficacious. This article elaborates on the rationale, use, and future directions of maintenance therapy after standard chemotherapy for advanced / metastatic non–small-cell lung cancer.

Key Words: *Carcinoma, Non-small-cell lung cancer; Lung neoplasms; Prognosis; Survival rate; Treatment outcome*

中文摘要

非小細胞肺癌維持治療的模式轉移

李浩勳

全身化療已成為晚期或轉移性非小細胞肺癌的標準治療，尤期是那些沒有表皮生長因子受體突變的病人。過去十年都沒有確實證據支持進行多於四至六個周期的化療。可是已有證據顯示全身性維持化療以及近期的標靶治療，可以為那些未受惠於標準化療的病人延緩病情惡化，更重要的是可以延長他們的生存期。病人接受完非培美曲塞的標準化療後再服用培美曲塞（pemetrexed）可以把生存期中位數增加2.8個月。化療後以簡單易用的埃羅替尼（erlotinib）作維持治療亦可把生存期中位數增加1.0個月。VEGF抗體貝伐單抗（bevacizumab）結合標準化療似乎同樣安全有效。對於晚期或轉移性非小細胞肺癌的病人接受完標準治療後所進行的維持治療，本文闡述其理念、用途及未來的發展方向。

INTRODUCTION

Systemic chemotherapy remains the standard treatment for unresectable or metastatic non–small-cell lung carcinoma (NSCLC), especially for patients who do not have mutated epidermal growth factor receptor (EGFR).[1] Recent large phase III randomised trials have shown that platinum-based combination chemotherapy yields a median survival of 8 to 11 months and a 1-year overall survival rate of 30 to 45%.[2-6] A representative meta-analysis has demonstrated that the use of systemic chemotherapy increased median survival by 2 months and improved 1-year overall survival rate by 10% when

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compared with best supportive treatment alone.[7] The American Society of Clinical Oncology has published its guidelines on the management of advanced NSCLC in 2003.[8] It pointed out that "first-line chemotherapy should be stopped at four cycles in patients who are not responding to treatment. The Panel consensus is that first-line chemotherapy should be administered for no more than six cycles...". It was updated in 2009 with a statement that "two-drug cytotoxic combinations should be administered for no more than six cycles" and "for patients who have stable disease or who respond to first-line therapy, evidence does not support the continuation of cytotoxic chemotherapy until disease progression or the initiation of a different chemotherapy prior to disease progression".[9] However the majority of these patients develop disease progression shortly after cessation of chemotherapy, including those who initially respond. Recently, maintenance therapy had been found conferring new hope to these patients, by delaying disease progression and prolonging survival. In this article, we therefore discuss the types and benefits of various forms of maintenance therapy.

MAINTENANCE THERAPY

Maintenance therapy can be subclassified into continuation maintenance therapy and switch maintenance. Continuation maintenance refers to the use of at least one of the agents given in first-line therapy beyond 4 to 6 cycles, in the absence of disease progression. Switch maintenance therapy denotes the initiation of a different agent not included as part of the first-line regimen after 4 to 6 cycles of initial therapy, in the absence of disease progression. It is also known as consolidation therapy. Clinical trial findings from both continuation maintenance therapy and switch maintenance therapy are described below.

Continuation Maintenance Chemotherapy

There are several published clinical trials addressing the role of continuation maintenance therapy for advanced/metastatic NSCLC (Table). First, Socinski et al[10] reported that the use of more cycles of paclitaxel and carboplatin did not produce a significant improvement in median survival compared to 4 cycles only (8.5 vs 6.6 months; $p = 0.63$). The extended therapy arm also resulted in a higher incidence of neuropathy. More recently, Belani et al[11] described the use of maintenance weekly paclitaxel in patients with non-progressing advanced / metastatic NSCLC after the initial therapy. Using 3 different schedules of paclitaxel and carboplatin, they noted only a statistically insignificant improvement in progression-free survival (38 vs 29 weeks; $p = 0.124$) and median survival (75 vs 60 weeks; $p = 0.243$). Later, von Plessen et al[12] demonstrated that 6 versus 3 cycles of vinorelbine and carboplatin did not translate into a meaningful prolongation of progression-free survival (21 vs 16 weeks; $p = 0.21$) or overall survival (32 vs 28 weeks; $p = 0.75$), but more blood transfusions were used in the extended treatment arm patients. The use of gemcitabine as continuation therapy after initial treatment with 4 cycles of gemcitabine and cisplatin is most promising.[13] Brodowicz et al[13] showed that maintenance therapy with gemcitabine resulted in a longer median time to progression (6.6 vs 5.0 months; $p < 0.001$) although there was no significant improvement in median survival (13 vs 11 months; $p = 0.195$). However a pre-planned subgroup analysis revealed that those with a better Karnofsky performance status score (>80) enjoyed a longer median survival (25.3 vs 12.2 months). In conclusion, continuation maintenance therapy was associated with a modest but non-significant improvement in progression-free survival and overall survival, at the expense of more chemotherapy-associated side-effects.

Table. Summary of trials on maintenance therapy.

Study	Year published	No. of patients	Median age of patients in study (years)	Study design	No. of cycles in experimental arm	No. of cycles in control arm
Socinski et al[10]	2002	230	63	Carboplatin + paclitaxel x 4 vs till PD UT	Continuous (to PD or UT)	4
Belani et al[11]	2003	130	66	Carboplatin + paclitaxel x 4 then randomised to weekly paclitaxel or placebo	Maintenance (to PD or UT)	4
von Plessen et al[12]	2006	297	64	Carboplatin + vinorelbine x 3 vs 6 cycles	6	3
Brodowicz et al[13]	2006	206	57	Carboplatin + gemcitabine x 4 then randomised to gemcitabine or placebo	Maintenance (to PD or UT)	4

Abbreviations: PD = disease progression; UT = unacceptable toxicity.

Continuation Maintenance Targeted Therapy

The treatment outcome of advanced / metastatic NSCLC has improved dramatically since the advent of targeted therapy. There are 4 commonly used effective targeting agents for this purpose, namely: EGFR–tyrosine kinase inhibitors (EGFR-TKIs) of erlotinib and gefitinib, bevacizumab — a humanised monoclonal antibody against vascular endothelial growth factor receptor (VEGFR), and cetuximab — a chimeric monoclonal antibody against EGFR. In particular, bevacizumab, cetuximab and erlotinib have been investigated in the maintenance therapy setting.

In the ECOG 4599 (Eastern Cooperative Oncology Group 4599) study,[14] 878 eligible patients with stage IIIB/IV non-squamous NSCLC were randomised to either paclitaxel plus carboplatin for 6 cycles or the same chemotherapy regimen with bevacizumab (15 mg per kilogram body weight) for 6 cycles followed by maintenance bevacizumab until disease progression. The objective response rate improved dramatically from 15% to 35% ($p < 0.001$) and there was prolongation of median survival by 2 months ($p = 0.003$). Owing to its anti-angiogenic nature, the treatment arm with bevacizumab also led to more fatal bleeding / thromboembolic events; 5 patients had pulmonary haemorrhage, two had other vascular events (cerebrovascular and gastrointestinal) and one had a probable pulmonary embolism. More recently, in AVAiL trial, Reck et al[15] investigated whether a lower dose of bevacizumab (7.5 mg per kilogram body weight) in combination with cisplatin and gemcitabine for 6 cycles followed by the same dose of maintenance bevacizumab demonstrated results that were comparable to the use of higher doses of bevacizumab (as used in the ECOG 4599 study). While the response rates and median progression-free survival in the chemotherapy and bevacizumab treatment were significantly better than in those who received chemotherapy plus placebo, both dosages of bevacizumab resulted in virtually the same outcomes. Median overall survival rates were similar in all treatment arms.[16]

At around the same time, SAiL, a phase IV study[17] in patients with advanced / metastatic non-squamous NSCLC, was also published with the aim of assessing safety and efficacy of initial and maintenance bevacizumab combined with several standard chemotherapy regimens. The latter included: platinum doublets, non-platinum doublets, monotherapy, switched chemotherapy, triplets and quadruplets, all used at the discretion of the participating institutions. Overall bleeding events and treatment-related deaths occurred in 4% and 3% of patients, respectively. The response rate was 51% in all chemotherapy groups and median survival ranged from 8.1 to 16.6 months; longer survival was noted in those who received switched chemotherapy and platinum doublets.

Another monoclonal antibody, cetuximab, was also investigated as initial and maintenance therapy. In the FLEX study,[18] patients were randomised to either cisplatin plus vinorelbine every 3 weeks for up to 6 cycles or the same chemotherapy regimens together with weekly cetuximab for up to 6 cycles followed by continuation of weekly cetuximab until disease progression. Patients who received additional cetuximab had a better response rate of 36%, as compared with 29% for those in the chemotherapy-alone group ($p = 0.01$). The former also survived longer (median, 11.3 vs 10.1 months), and the hazard ratio (HR) for death was 0.87 (95% confidence interval [CI], 0.76-1.00; $p = 0.044$). However, in pre-planned subgroup analysis, this benefit was not observed in Asian patients and those who had stage IIIB disease.

Another similar study was also aimed to look for any benefits when cetuximab was incorporated with taxane and carboplatin.[19] Patients were randomised to receive either paclitaxel or docetaxel (at the discretion of treating institution) plus carboplatin for up to 6 cycles, or the same chemotherapy regimens with weekly cetuximab for up to 6 cycles followed by maintenance cetuximab till disease progression (as in the FLEX study[18]). Both the progression-free and overall survival did not differ between these 2 treatment arms, although those who received cetuximab enjoyed a better response rate (25.7% vs 17.2% as assessed by an Independent Radiologic Review Committee; $p = 0.007$). In these 2 trials, as expected, more acne-like rashes and infusion-related reactions were encountered in cetuximab recipients.

Mok et al[20] also investigated the role of EGFR-TKI initially incorporated with chemotherapy followed by its maintenance use. In this phase II randomised controlled trial (FASTACT), sequential treatment with erlotinib or placebo was administered after gemcitabine and platinum in a 4-week cycle regimen for up to 6 cycles. In the absence of disease progression, patients continued erlotinib or placebo until disease progression or

unacceptable toxicity. Median progression-free survival was prolonged in those who received erlotinib while median overall survival was not different. Based on this encouraging result, a phase III trial (FASTACT-II) with a similar design has just completed patient accrual in September 2010 and its results are keenly awaited.

Switch Maintenance Therapy

Recently, switch maintenance therapy has gained the great popularity due to the absence of cross-drug resistance (in theory at least) due to the use of a different agent in the maintenance phase. Benefit has been demonstrated in large phase III trials using a different chemotherapeutic agent or a targeted drug.

In 2009, Fidias et al[21] reported on outcomes in a large phase III randomised controlled trial involving 309 eligible patients who received immediate docetaxel up to 6 cycles (after no progression with 4 cycles of gemcitabine plus carboplatin chemotherapy) versus delayed docetaxel at the time of progression. Only 5.2% of patients randomised to immediate docetaxel did not receive docetaxel whereas 37.2% of patients in the delayed arm did not receive docetaxel. The respective response rates to docetaxel in the 2 arms were similar (11.7 % vs 11.2%). Patients randomised to immediate docetaxel enjoyed a significantly longer median progression-free survival (5.7 vs 2.7 months; $p = 0.0001$). There was also a trend towards improved overall median survival in patients who received immediate docetaxel (12.3 vs 9.7 months; $p = 0.0853$). However, the median overall survival of patients in the delayed arm who actually received docetaxel was 12.5 months, which was identical to that in the immediate docetaxel arm. One of this study's most interesting findings was the notable difference in the percentage of patients receiving docetaxel in the 2 treatment arms — in the immediate treatment arm 94.8% received the drug whereas only 62.8% did so in the delayed arm. The major reason for not starting docetaxel in the delayed treatment arm was progressive disease with symptomatic deterioration coupled with the patient's decision. It seemed that patients were more likely and able to proceed to immediate treatment if they were healthier after initial chemotherapy.

In another large phase III double-blind, randomised controlled trial testing the role of pemetrexed in maintenance, 663 eligible patients whose stage IIIB/IV NSCLC did not progress after 4 cycles of non-pemetrexed platinum-based chemotherapy were randomised in a 2:1 ratio to pemetrexed or placebo once every 3 weeks, until disease progression.[22] The median number of maintenance pemetrexed and placebo treatments was 5.0 (range, 1-55) and 3.5 (range, 1-46), respectively. The progression-free survival was significantly longer in the maintenance pemetrexed group (median, 4.0 vs 2.0 months; HR = 0.60; 95% CI, 0.49-0.73; $p < 0.00001$). Overall survival was also longer in those receiving pemetrexed (median, 13.4 vs 10.6 months; HR = 0.79; 95% CI, 0.65-0.95; $p = 0.012$). Subgroup analysis revealed that improved progression-free and overall survival mainly occurred in patients with non-squamous histology. In particular, median overall survival in patients with non-squamous histology improved from 10.3 to 15.5 months (HR = 0.47; 95% CI, 0.37-0.60; $p < 0.0001$). However, in patients with squamous-type histology maintenance pemetrexed might actually jeopardise survival, declining from 10.8 months on placebo to 9.9 months on treatment, though this difference did not attain statistical significance (HR = 1.03; 95% CI, 0.71-1.49; $p = 0.896$). The difference of outcomes between non-squamous and squamous histological types may be attributed to the differential expression of thymidylate synthase (shown in-vitro to correlate with the sensitivity to pemetrexed). More patients suffered from manageable grade 3/4 neutropenia (3% vs 0%) and fatigue (5% vs <1%). A large phase III randomised controlled trial is currently ongoing to investigate whether the benefit of this form of maintenance therapy is also enjoyed by patients whose non-squamous NSCLCs do not progress after initial pemetrexed plus cisplatin chemotherapy.

In 2010, Cappuzzo et al[23] published a landmark study (SATURN) on the use of maintenance erlotinib. In all, 889 patients whose stage IIIB/IV NSCLC did not progress after initial treatment with 4 cycles of platinum-based chemotherapy were randomised in 1:1 ratio to receive either erlotinib or placebo, until disease progression. After a median follow-up of 11 months, median progression-free survival was significantly longer with erlotinib than with placebo (12.3 weeks vs 11.1 weeks; HR = 0.71; 95% CI, 0.62-0.82; $p < 0.0001$). Such benefit was also evident in patients with activating *EGFR* mutations and wild-type EGFR. Notably, this advantage accrued irrespective of histology, and was more prominent in those with adenocarcinomas. Using an intention-to-treat analysis, overall survival was significantly improved with erlotinib compared to placebo treatment (median, 12.0 vs 11.0 months; HR = 0.81; 95% CI, 0.70-0.95; $p = 0.0088$) and those

who did not harbour the *EGFR* mutations (HR = 0.77; 95% CI, 0.67-0.95; p = 0.0243). Survival data of patients with activating *EGFR* mutations were not available to date. Interestingly, non-responders after chemotherapy derived a greater survival benefit from maintenance erlotinib (median, 11.9 vs 9.6 months with placebo; HR = 0.72; 95% CI, 0.59-0.89; p = 0.0019). In contrast, those who had complete / partial responses to chemotherapy derived a trivial benefit (median, 12.5 vs 12 months with placebo; HR = 0.94; 95% CI, 0.74-1.20; p = 0.618). Erlotinib was well tolerated with manageable acne-like rash and diarrhoea and without unexpected toxicities.

Notably, in both the maintenance pemetrexed trial and the SATURN study, among patients initially randomised to placebo, only 67% and 64% respectively received post-study treatment after disease progression. Poor performance status and clinical deterioration at the time of disease progression that precluded post-study treatment could explain this finding. It seems that early maintenance therapy may have a role in controlling the disease and maintaining patient performance status. Other factors such as lack of access to second-line treatment or patient / physician preference may also have contributed to lower rates of post-study treatment.

CONCLUSION

In the last decade, maintenance therapy has become the focus of interest in the management of advanced / metastatic NSCLC. Continuation maintenance therapy with at least one of the agents in the initial regimen does not seem to improve outcomes and may increase toxicities. The new paradigm entails switch maintenance therapy with either erlotinib or pemetrexed. The result of incorporating anti-VEGFR monoclonal antibody into systemic chemotherapy during initial and maintenance treatment is promising. There are new dilemmas regarding the choice between EGFR-TKI and a new chemotherapeutic agent for maintenance. Whether immediate EGFR-TKI as opposed to delayed treatment is a better option also has to be resolved. The integration of anti-VEGFR and pemetrexed in the management of adenocarcinoma, a special entity of NSCLC, is also a subject for future research. Meanwhile, maintenance treatment in advanced / metastatic NSCLC remains a challenge.

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