Maintenance Chemotherapy for Advanced Non-small-cell Lung Cancer

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Abstract

Platinum-based combination chemotherapy, the current standard of care, enables modest improvements in survival and quality of life in patients with advanced non-small-cell lung cancer (NSCLC). In recent years, maintenance therapy in the form of either extended therapy or therapy with a different drug in patients deriving clinical benefit from initial treatment has been investigated. Extension of initial chemotherapy has shown improvements in time to tumour progression, but has not led to improved survival. Extension of chemotherapy is also associated with cumulative toxicities. Targeted agents such as bevacizumab and cetuximab can be extended until progression. However, the clinical benefits of continuing these agents until progression are unclear. Recently, a strategy of initiating treatment with a different drug following initial therapy has shown significant improvements in both progression-free survival and overall survival. Even though the applicability of this maintenance strategy may be limited to select patients, these data have established maintenance chemotherapy as a therapeutic option for advanced NSCLC patients.

Keywords

Maintenance therapy, non-small-cell lung cancer (NSCLC), pemetrexed, erlotinib, docetaxel

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Advanced stage of non-small-cell lung cancer (NSCLC) at presentation among many patients is the main reason for the poor survival observed in this disease. Systemic chemotherapy with platinum-based regimens is the current standard of therapy for patients with advanced NSCLC. However, such therapy provides only modest improvements in survival and quality of life. The median progression-free survival (PFS) with platinum-based chemotherapy is about five months and the overall survival (OS) is approximately 10 months. Various strategies including three-drug combinations did not result in a significantly superior outcome compared with two-drug platinum-based combinations. This led to the wide acceptance of the concept that we had reached a 'chemotherapy plateau' in advanced NSCLC. A strategy to improve outcomes has been to extend therapy or introduce a different drug in patients deriving clinical benefit from initial treatment. Recent clinical trial data have suggested that such a strategy can provide benefit for NSCLC patients. This article will consider the data and provide a perspective on the applicability of this strategy, termed maintenance therapy, in the management of advanced NSCLC patients.

Extended Chemotherapy

The guidelines published by the American Society of Clinical Oncology (ASCO) in 2004 state that first-line chemotherapy treatment should be limited to four cycles in non-responsive patients and six cycles in responsive patients (see *Table 1*).[1] One strategy to improve outcomes of patients with advanced NSCLC has been to continue treatment with the same chemotherapy. Trials evaluating this strategy either assessed higher number of cycles or continued therapy until progression. Earlier trials using older regimens to evaluate this strategy failed to show any improvement in time to tumour progression (TTP) or OS.[2–4]

The data with current therapeutic regimens suggest that prolonging systemic therapy may increase TTP, but does not increase OS. Socinski et al. compared four cycles of carboplatin and paclitaxel with therapy until disease progression.[5] The primary end-point of this study was one-year survival. The median survival and one-year survival with a defined number of cycles were 6.6 months and 28% versus 8.5 months and 34% in patients who received therapy until progression (p=0.63). von Plessen et al. assessed three versus six cycles of carboplatin and vinorelbine.[6] The primary end-point of this study was quality of life and survival. The study found no difference in any of the end-points between the two arms. Park et al. assessed four versus six cycles of chemotherapy in patients who had responding or stable disease after two cycles.[7] The primary end-point of this study was OS. This study demonstrated similar survival between patients who received four or six cycles. However, the study did observe a significant difference in TTP with six cycles of therapy: 6.2 versus 4.6 months (p=0.001). In a similar study, Barata et al. assessed four versus six cycles of therapy with carboplatin and gemcitabine and found improved survival in patients who received six cycles of therapy, although TTP was similar in the two arms.[8] The median

Table 1: Extended Chemotherapy

Study	Initial Regimen	Maintenance Strategy	PFS or TTP	OS
Socinski et al., 2002[5]	Carboplatin/paclitaxel – 4 cycles	Observation versus continued therapy until progression	Not reported	6.6 versus 8.5 months (p=0.63)
von Plessen et al., 2006[6]	Carboplatin/vinorelbine	3 versus 6 cycles	16 versus 21 weeks; p=0.21	28 versus 32 weeks (p=0.75)
Park et al., 2007[7]	Front-line cisplatin-based therapy	4 versus 6 cycles	4.6 versus 6.2 months; p=0.001	15.9 versus 14.9 months (p=0.46)
Barata et al., 2007[8]	Carboplatin/gemcitabine	4 versus 6 cycles	4 versus 5 months; p=0.077	7 versus 12 months (p=0.047)
Brodowicz et al., 2006[9]	Cisplatin/gemcitabine – 4 cycles	Observation versus continued gemcitabine	5 versus 6.6 months; p<0.001	11 versus 13 months (p=0.195)

OS = overall survival; PFS = progression-free survival; TTP = time to tumour progression.

Table 2: Extended Targeted Therapy

Study	Initial Regimen	Maintenance Strategy	PFS or TTP	OS
Sandler et al., 2006[10] (E4599)	Carboplatin/paclitaxel – 6 cycles with or without bevacizumab	Bevacizumab continued until progression in patients who received bevacizumab in the initial therapy	6.2 versus 4.5 months (p<0.001)	12.3 versus 10.3 months (p=0.003)
Reck et al., 2009[11] (AVAiL)	Cisplatin/gemcitabine – 6 cycles with 7.5mg/kg bevacizumab or 15mg/kg bevacizumab or placebo	Continued bevacizumab or placebo until progression	6.7 versus 6.1 months for 7.5mg/kg (p=0.003), 6.5 versus 6.1 months for 15mg/kg (p=0.03)	13.6 months for 7.5mg/kg, 13.4 months for 15mg/kg, 13.1 months for placebo (p=NS[a])
Pirker et al., 2009[12] (FLEX)	Cisplatin/vinorelbine with or without cetuximab	Cetuximab continued until progression in patients who received cetuximab in the initial therapy	4.8 versus 4.8 months (p=0.39)	11.3 versus 10.1 months (p=0.0441)
Mok et al., 2009[13]	Gefitinib versus carboplatin/paclitaxel (select patient population)	Gefitinib continued until progression; chemotherapy stopped at six cycles	12-month PFS rate 24.9% versus 6.7% (p<0.001)	18.6 versus 17.3 months (p=0.91)

a. Late-breaking abstract, Annual meeting of European Society of Medical Oncology, 2008. OS = overall survival; PFS = progression-free survival; TTP = time to tumour progression.

survival was seven months for patients who received four cycles and 12 months for those who received six cycles (p=0.047). Brodowicz et al. evaluated a slightly different strategy. Patients who had stable or responding cancer following four cycles of cisplatin and gemcitabine were randomised to maintenance gemcitabine versus observation.[9] The study was designed to assess TTP. The study demonstrated improved TTP with maintenance therapy (6.6 versus five months; p<0.001). The median survival was not statistically different between the two arms (13 versus 11 months; p=0.195).

Several observations can be made from analysing the data in terms of studies that assessed extension of chemotherapy. Extended therapy with platinum-based combinations is quite challenging. In the trial by Socinski et al., the median number of cycles with carboplatin and paclitaxel in both arms was four. Only 18% of the patients randomised to continued therapy received eight cycles or more. In addition, the rate of grade 2–4 neuropathy was higher in patients who received eight or more cycles. The cumulative nature of certain toxicities with drugs such as taxanes, vinca alkaloids and gemcitabine can limit the ability to deliver continued therapy. With the advent of pemetrexed, a drug that generally does not have cumulative toxicities, there is again an interest in assessing continued chemotherapy. Finally, of the studies listed above, only the study by Brodowicz et al. assessed the strategy of continuing therapy with just one drug. This study met its primary end-point of TTP but did not show an improvement in OS.

Maintenance/Extended Targeted Therapy

Targeted agents offer the possibility of continued therapy for a prolonged duration, as in many patients cumulative toxicities, commonly observed with cytotoxic agents, such as fatigue, haematological toxicities or neuropathy, are not observed with these agents. Randomised trials evaluating the addition of a targeted agent, such as epidermal growth factor receptor (EGFR) inhibitors or the vascular endothelial growth factor (VEGF) pathway inhibitors, to chemotherapy combination have included the option of continued therapy with the targeted agent (see *Table 2*).

Both E4599 and AVAstin in Lung cancer (AVAiL), two trials that evaluated the addition of bevacizumab, a monoclonal antibody targeting VEGF, to chemotherapy, included continued bevacizumab following six cycles of the combination.[10,11] E4599 demonstrated a survival advantage, while AVAiL demonstrated a PFS improvement with the addition of bevacizumab. It is unclear whether the continued bevacizumab contributed to these efficacy results as none of these studies had a study arm that terminated bevacizumab at the time the chemotherapy was stopped. In a similar design, the First-Line Erbitux in Lung Cancer (FLEX) trial assessed the addition of cetuximab, a monoclonal antibody targeting the EGFR, to chemotherapy combination followed by continued cetuximab.[12] This trial did demonstrate a survival advantage with the addition of cetuximab. However, it is again unclear whether the maintenance cetuximab contributed to these efficacy results, as there was no arm that terminated cetuximab at the same time as the chemotherapy.

Trials evaluating the addition of EGFR tyrosine kinase inhibitors (gefitinib and erlotinib) to chemotherapy did not show a survival advantage. However, in a recent trial that compared gefitinib with chemotherapy in a select group of patients (adenocarcinoma histology, Asian, never or light smokers), gefitinib was found to provide superior PFS in this population, particularly among patients

Table 3: Consolidation Chemotherapy/Targeted Therapy

Study	Initial Regimen	Maintenance Strategy	PFS or TTP	OS
Fidias et al., 2009[14]	Carboplatin/gemcitabine – 4 cycles	Docetaxel at progression versus immediate docetaxel	2.7 versus 5.7 months (p=0.0001)	9.7 versus 12.3 months (p=0.0853)
Ciuleanu et al., 2009[15]	Platinum-based therapy – 4 cycles	Placebo versus pemetrexed until progression	2.6 versus 4.5 months (p<0.0001 – non-squamous patients)	10.3 versus 15.5 months (p<0.0001)
Cappuzzo et al., 2009[17]	Platinum-based therapy – 4 cycles	Placebo versus erlotinib until progression	40 versus 53% at 12 weeks	11 versus 12 months (p=0.0088)

OS = overall survival.; PFS = progression-free survival; TTP = time to tumour progression.

whose tumours had EGFR mutations.[13] In this trial, gefitinib was continued until progression and the chemotherapy combination was continued for a maximum of six cycles. Again, this study did not evaluate gefitinib for a specific duration. However, as continued gefitinib and erlotinib are well tolerated and generally not associated with cumulative toxicities, both of these drugs can be continued until progression. These data suggest that continued therapy with agents that are convenient and well-tolerated in patients who are deriving clinical benefit may be a worthwhile strategy.

Consolidation Chemotherapy/Targeted Therapy

The strategy of consolidation therapy involves introduction of a non-cross-resistant therapy immediately after the initial therapy. Some experts have also termed this as early second-line therapy. Interest in this strategy developed following documentation of the advantages of treatment after progression of NSCLC following initial therapy.

Recently, three trials have shown an advantage with the introduction of a different agent following initial therapy (see *Table 3*). Fidias et al. assessed immediate docetaxel versus docetaxel at progression (delayed docetaxel) in NSCLC patients with stable or responding disease following four cycles of carboplatin/gemcitabine.[14] The median PFS was prolonged in the immediate docetaxel arm (5.7 versus 2.7 months; p=0.0001) and there was a trend (p=0.08) towards improvement in median survival with immediate docetaxel (12.3 versus 9.7 months). A few concerns about the trial should be considered. Of the 563 patients who started chemotherapy with carboplatin/gemcitabine, only 309 (55%) could be randomised to immediate or delayed docetaxel. Of the patients randomised to immediate docetaxel, 95% received at least one cycle, but of the patients randomised to delayed docetaxel, only 63% received any docetaxel. The major reasons for patients not receiving docetaxel in the delayed docetaxel arm of the study were progressive disease and patient decision. Review of patient data by the investigators revealed that many of these patients experienced significant symptomatic deterioration by the time they were diagnosed with progressive disease and were unable to receive docetaxel therapy. One possible reason for this observation may be the requirement of computed tomography (CT) evaluations only every three months. Considering that the median PFS in the delayed arm was 2.7 months, disease assessment with CT scans every three months is inadequate. It is also relevant to note that the survival of patients who received docetaxel in the delayed arm was equivalent to the survival of patients who received immediate docetaxel (12.5 months). These data raise the possibility that if the patients had been assessed more frequently and disease progression detected early, more patients in the delayed docetaxel arm could have received docetaxel and therefore derived clinical benefit. The quality of life analysis did not reveal a difference between the two arms.

Pemetrexed has also shown benefits in NSCLC patients with tumour progression following initial therapy. Therefore, this drug was also assessed as maintenance therapy in a large randomised trial.[15] Patients with advanced NSCLC who had not progressed after initial platinum-based therapy (which did not include pemetrexed) were randomised in a 2:1 manner to pemetrexed with best supportive care (BSC) versus placebo with BSC. The primary end-point of the trial was to demonstrate an improvement in PFS with pemetrexed. Six hundred and sixty-three patients were randomised to pemetrexed (441) and placebo (222). The median PFS for patients who received pemetrexed and placebo was four versus two months (p<0.00001). It has become apparent in this and other studies that the clinical benefit from pemetrexed is restricted to non-squamous patients.[16] According to a pre-defined analysis based on histology, the median PFS in non-squamous patients treated with pemetrexed was 4.4 months versus 1.8 months in the control arm (p<0.00001), whereas no difference in PFS was observed in squamous cell patients. The OS was also significantly improved with maintenance pemetrexed. The median survival with pemetrexed in the overall population was 13.4 months and in the non-squamous patients was 15.5 months. These were both significantly superior to patients who received placebo (10.6 months overall, 10.3 months non-squamous). In this study, 67% of the patients on the placebo arm received further therapy; however, only 19% of these patients received pemetrexed. The results of this study show that pemetrexed provides benefit in patients who have derived benefit from initial therapy. Based on these results, the US Food and Drug Administration (FDA) has approved pemetrexed for maintenance therapy in non-squamous NSCLC patients. However, it is not certain that the survival benefit would have been observed if a higher percentage of patients in the placebo arm had received pemetrexed. Therefore, this study fails to adequately address the question of timing of pemetrexed following initial treatment. It would be interesting to know the PFS and survival of patients on the placebo arm who received pemetrexed at progression. In addition, it is unclear whether similar benefits would be observed with maintenance pemetrexed in patients who receive pemetrexed-based initial therapy.

With a similar design to the pemetrexed trial, a global phase III study (SATURN) assessed the efficacy of maintenance erlotinib in NSCLC patients.[17] Patients with non-progressive NSCLC following platinum-based chemotherapy were randomised to erlotinib or placebo. One thousand, nine hundred and forty-nine chemotherapy-naïve patients were enrolled on the trial. Following completion of initial chemotherapy, 889 patients were randomised to erlotinib or placebo. The primary end-point of the study was PFS. PFS was significantly prolonged with maintenance erlotinib (hazard ratio [HR] 0.71; p<0.0001). In a recently presented update, survival (HR 0.81; p=0.0088) was also significantly improved with maintenance erlotinib. Again, in this study only 21% of the patients on the placebo arm received any

EGFR tyrosine kinase inhibitors. Therefore, one has to conclude that this study, like the pemetrexed study, does not adequately address the timing of erlotinib following initial therapy. The SATURN trial included quality of life analysis. This analysis showed that time to pain and time to analgesic use was prolonged with maintenance erlotinib.

Therefore, these three studies suggest that immediate therapy with a different agent can provide clinical benefit. However, the design of these studies raises questions in terms of implementing this strategy as standard of care. Therefore, it is unclear whether frequent assessments to detect progression and treating NSCLC patients with effective second-line therapy at the earliest evidence of progression could provide the same benefits as observed with early therapy with a non-cross-resistant agent following initial therapy. In addition, it is important to note that front-line recommendations for non-squamous NSCLC patients have evolved over the last few years. Pemetrexed-based therapy is now considered the most effective chemotherapy in patients with non-squamous histology and bevacizumab is commonly combined with chemotherapy in non-squamous patients.[10,18] None of the maintenance studies assessed this strategy in patients who received pemetrexed-based therapy and/or bevacizumab therapy as initial therapy. Furthermore, it is unclear whether continued therapy with pemetrexed after completion of four to six cycles of pemetrexed-based therapy provides any additional benefit. In squamous-cell NSCLC patients the front-line recommendations have remained the same and therefore the clinical trial data from these trials are more applicable to squamous cell patients.

Conclusions

Recent data have shown that extending therapy can provide benefits to advanced-stage NSCLC patients. The best evidence of benefit was found in trials that assessed the introduction of a different agent following initial therapy. Based on all of the available data, maintenance therapy should be considered for patients who have derived clinical benefit from initial therapy and continue to have a good performance status. It is important to note that the applicability of this strategy is limited, as suggested by the observations that only 50–60% of the patients who completed front-line therapy could be randomised to the maintenance portion of the Fidias and SATURN trials.[14,17] The maintenance studies also highlight the importance of frequent assessments and early detection of progression in patients who are being monitored without therapy after completion of initial treatment. ■

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