Maintenance chemotherapy in non-small cell lung cancer

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introduction

The role of chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) has been established only in the last decade. The cornerstone is represented by the 1995 meta-analysis, which demonstrated the usefulness of platinum-based chemotherapy in this setting [1]. In spite of the improved results of the last years using new drugs-combinations, chemotherapy still remains a palliative approach whose efficacy has to be balanced with its acute and cumulative toxicity. For these reasons, the duration of the chemotherapeutic treatment is a field of debate between clinical researchers and new chemotherapy strategies have been investigated, including maintenance chemotherapy.

is there an optimal duration for first-line chemotherapy in advanced NSCLC?

The 1997 guidelines, issued by the American Society of Clinical Oncology (ASCO) [2] suggested that chemotherapy should be administered for no more than 8 cycles in patients with advanced NSCLC, even if this conclusion was based only on one controlled trial [3]. In this study, 74 patients with stable disease after 2 or 3 cycles of methotrexate, doxorubicin, cyclophosphamide, and lomustine (MACC regimen) were randomised to further therapy or to best supportive care. The study failed to demonstrate any survival advantage with the continuous treatment [3]. More recently, a randomised study of 3 versus 6 courses of mitomycin, vinblastine and cisplatin was performed in 308 patients with advanced NSCLC [4]. Seventy-two percent of the 155 patients randomised to 3 courses completed the treatment. In the 153 patients randomised to 6 courses, 73% completed 3 courses and 31% completed 6 courses. Median survival was 6 versus 7 months, respectively, and 1-year survival was 22% versus 25% (P = 0.2). Median duration of symptom relief was 4.5 months in both arms, and 8% versus 18% had continuing symptom relief (P = 0.4).

Quality-of-life (QoL) parameters were the same or improved for patients randomised to only 3 courses. The authors concluded that there is no evidence for additional clinical benefit by continuing MVP chemotherapy beyond 3 courses. In 2002, Socinski et al. published a phase III trial comparing 4 cycles of carboplatin and paclitaxel (arm A) to a continuous treatment of the same schedule of chemotherapy until progression (arm B). Two-hundred and thirty patients in stage IIIb/IV were randomised. Fifty-seven percent of arm A patients completed 4 courses of therapy. Forty-two percent received 5 or more cycles; 18% received 8 or more cycles. Overall, response rates were 22% and 24% for arms A and B, respectively (P = 0.80). Median survival time and 1-year survival rates were 6.6 months and 28% for arm A and 8.5 months and 34% for arm B, respectively (P = 0.63). Haematologic and non-haematologic toxicities were similar between the two arms, except for neuropathy which worsened increasing the number of cycles. There was no difference in QoL. In this study, there was no benefit in survival, response rates, or QoL, to continuing treatment beyond four cycles of chemotherapy [5].

Both these trials were included in the updated ASCO guidelines for the treatment of unresectable NSCLC published in January 2004 [6]. Recognizing that the optimal duration of chemotherapy remains a matter of debate, Pfister et al. noted that prolonged chemotherapy can lead to cumulative toxicity, with no proven advantage in efficacy. In fact, the majority of patients failed to have a major response, or became intolerant of chemotherapy, by the third or fourth cycle. Furthermore, in light of new evidence that supports the use of second-line chemotherapy at the time of recurrence, the Panel consensus was to change the prior recommendation, and advocate no more than 6 cycles of initial chemotherapy, even in patients who have responded to treatment. However, neither trial addressed the more specific question of whether patients who are responding to chemotherapy, and tolerating chemotherapy well, benefit from the prolongation of the treatment.

Further support to the ASCO recommendations is provided by a Norwegian trial comparing 3 versus 6 courses of carboplatin and vinorelbine in advanced NSCLC [7]. Among the 297 patients, survival curves were virtually identical for both groups (HR 1.07, 95% CI 0.84–1.37). Median survival was 28 weeks and 32 weeks for 3 and 6 courses, respectively (P = 0.58). Estimated 1-year survival was 24% versus 26%. Estimated 2-year survival was 24% versus 26%.

is there a role for maintenance chemotherapy in advanced NSCLC?

Maintenance chemotherapy is the prolongation of chemotherapy duration with the administration of additional chemotherapy at the end of a defined number of initial cycles. More recently, a randomised study of 3 versus 6 courses of mitomycin, vinblastine and cisplatin was performed in 308 patients with advanced NSCLC [4]. Seventy-two percent of the 155 patients randomised to 3 courses completed the treatment. In the 153 patients randomised to 6 courses, 73% completed 3 courses and 31% completed 6 courses. Median survival was 6 versus 7 months, respectively, and 1-year survival was 22% versus 25% (P = 0.2). Median duration of symptom relief was 4.5 months in both arms, and 8% versus 18% had continuing symptom relief (P = 0.4).

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Maintenance chemotherapy is the prolongation of chemotherapy duration with the administration of additional chemotherapy at the end of a defined number of initial cycles.
chemotherapy cycles, after achieving a maximum tumour response in an individual patient. Patients achieving a partial or complete response after initial chemotherapy, also referred to as induction chemotherapy, may be candidates to maintenance chemotherapy. In the absence of significant toxicity, maintenance chemotherapy is continued either for a defined time or until evidence of progressive disease. Maintenance chemotherapy consists of either a drug included in the induction regimen or another non-cross resistant agent at a relatively low dose. In published trials of maintenance chemotherapy, the population is heterogeneous: in some studies, patients achieving a complete or partial response are candidates to receive maintenance chemotherapy, while in other studies, patients with stable disease at the end of induction chemotherapy are also eligible for the maintenance therapy.

The rationale for maintenance chemotherapy is provided by the Goldie and Coldman hypothesis stating that the early use of non-cross-resistant agents might increase the probability of killing more cancer cells before resistance arises [8], and by the Day model indicating that the most active drug/ regimens should be used as a consolidation treatment to optimize results [9]. To date, few clinical trials have assessed the role of a third-generation agent as maintenance therapy in advanced NSCLC (Table 1). In a randomised trial, Westeel et al. compared maintenance vinorelbine therapy with observation in stage IIIIB-IV NSCLC patients who responded to induction treatment with mitomycin-ifosfamide-cisplatin (MIC) [10]. A total of 573 patients were registered, of whom 227 responded to induction treatment and 181 were randomized 1:1 to maintenance vinorelbine or observation. 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 in progression-free survival between the two arms ($P = 0.32$). This disappointing result is consistent with the poor activity reported for vinorelbine in second-line NSCLC following platinum-based chemotherapy.

At the 2005 ASCO meeting, Belani reported an update of a randomised phase III trial exploring the feasibility of maintenance therapy with weekly paclitaxel vs. observation, following three cycles of carboplatin plus paclitaxel as initial therapy [11, 12]. Of the 444 patients enrolled, 141 (77%) entered the maintenance chemotherapy phase. Median survival was 76 weeks versus 29 weeks in patients receiving maintenance chemotherapy and in the observation arm, respectively. One- and 2-year survival rates were 69% and 33% versus 25% and 9%, respectively. The improved survival was associated with minimal toxicity. Despite a longer time to progression and median survival time in patients randomized to receive maintenance therapy, no conclusions can be drawn because the trial was designed to determine the optimal schedule for the administration of the carboplatin plus paclitaxel combination and not powered to address the role of maintenance therapy with weekly paclitaxel.

Krzakowski and co-workers conducted a randomized phase III trial comparing maintenance therapy with gemcitabine plus best supportive care vs. best supportive care in patients without progressive disease following initial therapy with cisplatin and gemcitabine [13]. Preliminary results suggest a significant benefit of maintenance therapy with gemcitabine in terms of time to progressive disease 6.6 vs. 5 months, $P < 0.001$) and a significantly longer overall survival in the subset of patients with a baseline PS > 80, with no differences in quality of life between the two arms. This positive result may be partially related with the selection of patients who achieve disease control with the induction cisplatin-gemcitabine therapy and who are more likely to benefit from additional maintenance chemotherapy with gemcitabine.

A multicenter phase II study with two different schedules of docetaxel and gemcitabine and a sequence of cisplatin-gemcitabine followed by docetaxel has also been presented as preliminary results at the 2005 ASCO meeting. One-hundred and sixty-three patients were randomly assigned to gemcitabine and docetaxel, days 1 and 8 (arm A), or days 1 and 15 (arm B), or to cisplatin-gemcitabine for 3 cycles followed by docetaxel every 3 weeks till progression. In the sequence arm, among 54 patients, 1-year survival was 60%, median survival 16.9 months (95% CI 9.8–22.2), and median time to progression was 10.3 months (95% CI 6.6–13.6). In terms of efficacy, arm A and arm C appeared to be more active and should be compared in a phase III setting [14].

Preliminary results of a randomised phase III study in stage IV NSCLC patients treated with 2 cycles of cisplatin/gemcitabine (GC) followed by either 3 additional cycles of GC (arm A) or gemcitabine alone (arm B) were recently presented at ASCO.

### Table 1. Randomised trial of maintenance chemotherapy in advanced NSCLC

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Regimen</th>
<th>RR (%)</th>
<th>MS (mo)</th>
<th>1-yr S (%)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Westeel 2003</td>
<td>181</td>
<td>MIC→4</td>
<td>37</td>
<td>12.5</td>
<td>50.6</td>
<td>0.65</td>
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<tr>
<td></td>
<td></td>
<td>MIC→4→VNR</td>
<td>37</td>
<td>10.2</td>
<td>42.2</td>
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<tr>
<td>Belani 2005</td>
<td>444</td>
<td>CBDCA-TAX→TAX</td>
<td>NR</td>
<td>17.7</td>
<td>69</td>
<td>0.016</td>
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<tr>
<td>Krzakowski 2004</td>
<td>215</td>
<td>CBDCA-TAX</td>
<td>NR</td>
<td>6.8</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GP→GEM</td>
<td>NR</td>
<td>13</td>
<td>NR</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>GP→observation</td>
<td>NR</td>
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<tr>
<td>Rinaldi 2005</td>
<td>163</td>
<td>GEM-TXT d 1 &amp; 8</td>
<td>20.8</td>
<td>12.3</td>
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<tr>
<td></td>
<td></td>
<td>GEM-TXT d 1 &amp; 15</td>
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<td>9.3</td>
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<tr>
<td></td>
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<td>29.6</td>
<td>16.9</td>
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</table>

MVP: mitomycin, vinblastine, cisplatin; CBDCA: carboplatin; TAX: paclitaxel; VNR: vinorelbine; MIC: mitomycin, ifosfamide, cisplatin; GEM: gemcitabine; TXT: docetaxel; GP: gemcitabine, cisplatin.
interferon induction therapy. Maintenance with interferon alpha 2a [18], vinorelbine and consolidation therapy was docetaxel, with II trial where the concomitant chemotherapy was cisplatin-cisplatin-etoposide [16]. Similar results were achieved in a phase only in substitution of consolidation docetaxel for continued patients with identical concurrent chemoradiotherapy, differing 9019 historical control, in a cohort of 50 stage IIIB NSCLC stage IIIB. The updated results in 83 patients report a 5-year demonstrated the efficacy of consolidation docetaxel following NSCLC [15].

Moving to an earlier stage, the SWOG study S9504 demonstrated the efficacy of consolidation docetaxel following concurrent cisplatin-etoposide and thoracic radiotherapy in stage IIIIB. The updated results in 83 patients report a 3-year survival of 29%. These data compare favourably with the SWOG 9019 historical control, in a cohort of 50 stage IIIIB NSCLC patients with identical concurrent chemoradiotherapy, differing only in substitution of consolidation docetaxel for continued cisplatin-etoposide [16]. Similar results were achieved in a phase II trial where the concomitant chemotherapy was cisplatin-vinorelbine and consolidation therapy was docetaxel, with a median survival of 30.8 months [17].

Several phase II trials evaluated other agents as maintenance therapy in advanced NSCLC following a platinum-based induction therapy. Maintenance with interferon alpha 2a [18], interferon z [19], bexarotene [20], or UFT [21] seems feasible, but it is unclear whether these agents are really effective. Several trials are currently evaluating new chemotherapeutic agents and molecularly targeted agents following a standard platinum-based first-line chemotherapy. Based on the efficacy of pemetrexed in second-line NSCLC, a randomised phase III, double-blind study of maintenance pemetrexed plus best supportive care versus placebo plus best supportive care is currently ongoing (NCT 00102804 trial). A randomised phase III trial led by the European Organization for Research and Treatment of Cancer (EORTC) is currently evaluating maintenance gefitinib (ZD 1839) vs placebo in advanced NSCLC (EORTC 08021 trial). Patients with stable or responsive disease after first-line platinum-based induction chemotherapy are randomly assigned to receive gefitinib or placebo once daily, until disease progression or unacceptable toxicity. A similar randomised trial is ongoing in the U.S.A. (NCT 00090675 trial).

conclusions

Maintenance chemotherapy is feasible and may provide additional benefit after standard first-line platinum-based chemotherapy given for up to six cycles, also referred to as induction chemotherapy. A benefit is likely to be observed when maintenance chemotherapy consists of an agent that has proven active in the induction phase. In fact, induction chemotherapy can be considered as an in vivo chemosensitivity assay to test the sensitivity of each individual patient to the drugs used in the induction phase. Further evaluation of maintenance chemotherapy using one of the drugs administered in the induction phase, only in selected responding patients, is warranted in randomised trials. In addition, results of randomized trials assessing new biologic agents are awaited with interest.

In conclusion, current standard treatment for advanced NSCLC patients with good performance status includes first-line treatment with a platinum-based two-drug regimen for a maximum of 6 cycles in the absence of unacceptable toxicity or progressive disease. At present, maintenance chemotherapy must still be considered investigational.

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