WEEKLY DOCETAXEL AS SECOND-LINE THERAPY IN NON-SMALL CELL LUNG CANCER: A PHASE II STUDY

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Introduction: Single-agent docetaxel is active as second-line chemotherapy in non-small cell lung cancer (NSCLC) pretreated patients; seven phase II studies have shown response rates of about 20% and 9 months of median survival. Two phase III studies documented a survival benefit at 1 year compared to BSC and vinorelbine or ifosfamide. Recent trials indicate acceptable activity and a good safety profile of weekly docetaxel with doses of 25-43 mg/m². The aim of our study was to confirm this evidence and to evaluate activity and toxicity of weekly docetaxel at the dose of 40 mg/m².

Patients and methods: Twenty-one patients with NSCLC entered the study (7 stage IIIB and 14 stage IV): 13 males and 8 females. Median age was 66 years (range, 53-75). ECOG was 0 in 6, 1 in 9 and 2 in 6 patients. All patients were pretreated with a first-line chemotherapy (13 patients progressed soon after the first line); 6 of them received palliative radiotherapy on the chest. The treatment consisted of weekly docetaxel, 40 mg/m² in 1 hr for six weeks with two weeks of rest (1 cycle). A total of 87 administrations was delivered (median, 4; range, 1-12).

Key words: chemotherapy, docetaxel, lung cancer, second line.

Introduction

Recent meta-analysis of randomized clinical trials has demonstrated a small but significant 10% survival benefit at 1 year for patients treated with cisplatin-based regimens in comparison to local-regional treatment or BSC.² Three data confirmed that cisplatin remains the most important drug as a basis for combination chemotherapy in NSCLC. Overall response rates with modern regimens are in the range of 30-40%, median survival is approximately 8-10 months, with 1-year survival rates of 30-40%.³,⁴ Despite these results, all responding patients experience a relapse and die for distant metastases. Therefore, a high proportion of patients may be candidate for second-line chemotherapy during the course of their disease, and a number of phase II studies on second-line therapy are available.⁵ Response rates in almost all trials were less than 10%, without clear information on survival. Among various agents, docetaxel has been more extensively investigated for the second-line treatment of NSCLC.⁵ Two phase III studies (TAX 317 and TAX 320) demonstrated that docetaxel, 75 mg/m² every 3 weeks, despite low response rates (6-7%), provided a survival gain at 1 year compared with BSC and vinorelbine or ifosfamide.⁶,⁷ Recently, the weekly administration of docetaxel has been explored in phase I studies.⁸,⁹ Hainsworth et al. showed that this schedule provides a good safety profile, particularly for the low myelosuppression. The recommended dose of weekly docetaxel was 36 mg/m². However, many phase II studies have been planned with weekly docetaxel as second-line therapy in these last 3 years, with different doses (from 25 to 43 mg/m²) and different response rates (from 0-26.7%; median, 12%).¹⁰,¹¹ (Table 1).

The aim of our study was to evaluate activity and toxicity of weekly docetaxel as second-line therapy in NSCLC at the dose of 40 mg/m², with particular attention to safety of the schedule.

Patients and methods

Eligibility criteria

Patients with stage IIIB and IV NSCLC progressive disease after a first-line chemotherapy entered the study. Radiotherapy on the chest was permitted only if completed at least 6 months before. Other selection criteria included: a) ECOG performance status 0-2, b) adequate liver, renal and bone marrow function, c) life expectancy of at least 3 months, d) age ≤ 75 years. Patients with bone metastases as the only measurable site of disease...
and patients with symptomatic brain metastases were excluded from the study. Staging procedures included blood chemistries, physical examination, chest X-ray, chest-abdomen CT scan, bone scan and any other test to identify the extent of disease was performed. An informed oral consent was obtained from each patient.

**Study design**

Docetaxel was administered as a 1-hr intravenous (iv) infusion at the dose of 40 mg/m² for six consecutive weeks, followed by a 2-week rest (one course). All patients received an abbreviated premedication with dex-amethasone 8 mg im 12 hrs and 1 hr before docetaxel, and again 12 hrs following docetaxel administration. Response and toxicity were the primary end points. Response was assessed according to WHO standard criteria after 1 course or at least 5 administrations. Toxicity was evaluated after every weekly administration according to NCI criteria. Overall survival was calculated as the interval between day 1 of the first cycle and the date of death or, in the absence of its assessment, last follow-up for patients still alive. Median survival was evaluated according the Kaplan-Meier method. According to the optimal two-stage design, for a target activity level of at least 20% response rate, 2 objective responses should be observed in the first 21 assessable patients (alpha and beta error probabilities 0.05 and 0.010, respectively).

**Results**

From January 2000 to December 2001, 21 patients with locally advanced and metastatic NSCLC entered the study (7 stage IIIB and 14 stage IV): 13 males and 8 females. All patients had been pretreated with a first-line chemotherapy: 18 with cisplatin/gemcitabine, 1 with cisplatin/etoposide, 1 with gemcitabine, 1 with gemcitabine/vinorelbine (6 of them received palliative radiotherapy on the chest). Thirteen patients were considered "refractory" to chemotherapy (the disease progressed soon after the first-line treatment). Median age was 66 years (range, 53-75).

The treatment consisted of weekly docetaxel 40 mg/m² in 1 hr for 6 weeks with 2 weeks of rest (1 cycle). A total of 87 administrations was delivered (median, 4; range, 1-12). Only 1 patient completed two cycles; 6 patients completed 1 cycle and 5 patients underwent 5 administrations. The study was stopped early for severe toxicity: only 11 out of 21 patients completed at least 1 course or 5 administrations with subsequent instrumental evaluation.

No complete or partial remission was observed; 2 minor responses (9.5%), 1 stable disease (5%) and 8 progressive diseases (38%) were documented. Ten patients (47.5%) dropped out the study: 7 due to severe toxicity and 3 due to early death. Median survival was 3 months (range, 1-17), and 1-year survival was only 9.5%.

Toxicity was as follows: grade 4 diarrhea in 1 patient; grade 3 asthenia in 8 (38%), grade 3 stomatitis in 2; grade 3 neutropenia in 1. Hypersensitivity reactions occurred in 2 patients (1 with ventricular escapes, cardiopalmus and syncope, and 1 with dyspnea, lips edema and flushing). No treatment-related death occurred. Only 1 patient is alive at this writing.

**Discussion**

In six single-agent phase II studies of docetaxel in NSCLC, more than 270 patients were treated at the dose of 60, 75, and 100 mg/m², with response rates of 8 to 21% (median survival, 5.7 to 11.2 months and 1-year survival rates of 18-41%). However, when docetaxel was administered with a 21-day schedule, myelosuppression (neutropenia and thrombocytopenia) was frequently the main toxicity. The use of weekly docetaxel seems to induce a low incidence of hematological toxicity; otherwise, many patients experience asthenia with this schedule. In the last 3 years, a few trials with weekly docetaxel as second-line in NSCLC have been planned and published, mainly as abstracts. In phase I studies, the recommended dose of docetaxel was 36 mg/m²; however, available phase II trials used doses ranging from 25 to 43 mg/m², with response rates of 0% to 26.7%. To the best of our knowledge, our study is the third that used a dose of 40 mg/m² for six consecutive weeks with 2 weeks off. In another trial by Lin, docetaxel was delivered for 3 weeks with 1 week of rest.

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**Table 1 - Studies with weekly docetaxel as second line in NSCLC**

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. patients/assessable for response</th>
<th>Schedule mg/m²</th>
<th>Objective response</th>
<th>Median survival (months)/1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lilienbaum RC</td>
<td>31/30</td>
<td>36 for 6 weeks</td>
<td>10</td>
<td>8/31</td>
</tr>
<tr>
<td>Serke M</td>
<td>36/36</td>
<td>36 for 6 weeks</td>
<td>26.7</td>
<td>12/46</td>
</tr>
<tr>
<td>Gomez RG</td>
<td>24/9</td>
<td>26/15</td>
<td>11</td>
<td>6/NR</td>
</tr>
<tr>
<td>Garzia-Lopez</td>
<td>56/30</td>
<td>40 for 3 weeks with 1 week off</td>
<td>13.3</td>
<td>NR</td>
</tr>
<tr>
<td>Lin C</td>
<td>18/16</td>
<td>25 for 12 weeks</td>
<td>8</td>
<td>5.9/17</td>
</tr>
<tr>
<td>Gervais R</td>
<td>103/NR</td>
<td>35 for 3 weeks with 1 week off</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Azzouz A</td>
<td>63/NR</td>
<td>40 for 6 weeks</td>
<td>4.8</td>
<td>5.2/NR</td>
</tr>
</tbody>
</table>

NR, not reported.
In our trial, we did not observe any objective response, with 2 minor responses, 1 stable disease and 8 progressive disease. Median survival was only 3 months, and 1-year survival 9.5%. These results are unsatisfactory but we must consider that 13 patients (62%) progressed soon after the completion of the first line. Eleven of 21 patients completed 1 course or at least 5 administrations. These data do not allow us to draw final conclusions on the activity of this schedule, but we were forced to stop the trial early for the severe toxicity reported by most patients.

As shown in Table 2, the main toxicity was asthenia in 38% of patients. Other toxicity included: grade 4 diarrhea in 1 patient, grade 3 stomatitis in 2 patients, grade 3 neutropenia in 1 patient, and allergic reactions in 2 patients. Furthermore, 1 patient experienced an acute lung edema after the first administration, and 3 patients died during chemotherapy. Even though the deaths were not related to the treatment, we decided to stop the accrual for ethical reasons.

What are the possible explanations for the severe toxicity? In our study, the median age (66 years; 10 patients were ≥70) was a little higher than in other trials and coexisting illnesses might have contributed to enhance side effects in elderly patients. We use an abbreviated premedication with dexamethasone, 8 mg im 12 hrs and 1 hr before docetaxel and again 12 hrs following docetaxel administration. The results of Briasoulis et al. support the evidence that treatment with weekly docetaxel does not require protracted use of dexamethasone. However, we hypothesized that the steroid dose may not be enough when this agent is delivered at over 36 mg/m². The ECOG of our patients was 2 in 6 (28.5%) and 1 in 9 (43%) patients. These data do not seem particularly unfavorable to decide the use of a single agent in second line. However, the high number of side effects shows that a better patient selection should be performed when using a second line in NSCLC.

In conclusion, we think that our study, even though has not provided clear information on the activity of the schedule, shows that weekly docetaxel over the recommended dose (36 mg/m²) may enhance the severity of side effects and patient compliance (this evidence confirms the higher toxicity reported by Garcia-Lopez et al. with a schedule at 43 mg/m²). These results, in terms of responses and toxicity, diverge from those reported by Valerio et al. and Gervais et al. It is difficult to understand the toxicities of the study by Lin in his trial, no patient had grade 4 neutropenia or thrombocytopenia, but no other toxicity was reported). We may have unintentionally selected patients with a worse prognosis. However, the number and severity of side effects should induce the oncologist to consider with greater attention the increase in weekly docetaxel dose over 36 mg/m² and the “target” of patients to treat in second line, especially those with a short disease-free interval or none. Moreover, to date we do not know whether weekly docetaxel (and at which doses) is really favorable to decide the use of a single agent in second line.

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References


