Single-Agent Paclitaxel in the Treatment of Advanced Non-Small Cell Lung Cancer

MARK A. SOCINSKI

The Multidisciplinary Thoracic Oncology Program, University of North Carolina, Chapel Hill, North Carolina, USA

Key Words. Paclitaxel - NSCLC

ABSTRACT

Paclitaxel was the first identified member of a new class of anticancer drugs known as the taxanes. This compound has significant single-agent activity against a number of solid tumors including nonsmall cell lung cancer (NSCLC). In the first-line setting, single-agent paclitaxel has been studied on a number of different schedules and dose levels. Initial studies were done on the 24-h infusion schedule with doses of 200-250 mg/m². Response rates were 21%-24%. Median survival ranged from six to nine months with one-year survival rates of 38%-42%. The major toxicity of this infusion schedule was myelosuppression, mainly neutropenia. Subsequent single-agent studies employed shorter infusion durations (three hours), with doses ranging from 175-225 mg/m². The cumulative experience of the 3-h infusion schedule shows an overall response rate of 28.5% with median survival of 6-11 months and a one-year survival of 37.5%. Similar results were obtained in the one study examining the 1-h infusion schedule with doses ranging from 175-225 mg/m². The major toxicities of the shorter infusion schedule include neutropenia, neuropathy, and myalgia/arthritis syndrome. Weekly administration of paclitaxel also showed significant activity in advanced, metastatic NSCLC. Overall response rates have ranged from 30%-56% in the phase I/II setting with one-year survival rates of 42%-53%. A recently completed phase III trial comparing single-agent paclitaxel at 200 mg/m² over three hours every three weeks to best supportive care (BSC) in advanced or metastatic NSCLC has shown a survival advantage for the single-agent paclitaxel arm (median survival 6.8 months for paclitaxel versus 4.8 months for BSC, \( p = 0.045 \)). An ongoing phase III trial is comparing single-agent paclitaxel to the combination of carboplatin and paclitaxel (CALGB 9730) in advanced, metastatic NSCLC. Paclitaxel has also been studied in the second-line setting. Infusion schedules have ranged from 1 h, 24 h and 96 h on an every-three-week schedule. Weekly paclitaxel has also been evaluated in the second-line setting. Although the overall experience is limited, response rates have ranged from 0%-38%. The overall role of single-agent paclitaxel in prolonging survival and improving quality of life remains uncertain in this setting.

The cumulative experience of single-agent paclitaxel in advanced, metastatic NSCLC suggests that it is a highly active cytotoxic agent in this setting. The consistent finding of a 35%-40% one-year survival rate is notable. The major toxicities include neutropenia, neuropathy, and myalgia/arthritis syndrome. Given the overall activity and impact on survival along with an acceptable toxicity profile, single-agent paclitaxel warrants comparison to other active agents and combination regimens in advanced, metastatic NSCLC. The Oncologist 1999;4:408-416

INTRODUCTION

In 1963, a crude extract from the bark of the Pacific yew tree (Taxus Brevifolia) was found to have significant preclinical activity against a number of tumors. The active ingredient in that crude extract was subsequently identified as paclitaxel [1]. This compound was the first identified member of a new class of anticancer agents known as the taxanes. In 1979, paclitaxel’s unique mechanism of action was identified [2]. Paclitaxel was found to promote the polymerization of tubulin and to produce extraordinarily stable and dysfunctional microtubules, thereby causing cell death by disrupting normal microtubular dynamics required for cell division and vital interphase processes [2-5]. When paclitaxel was demonstrated to have significant activity in murine and human tumor
xenografts in the National Cancer Institute tumor screen [4], interest in the clinical development of the drug heightened and initial phase I trials were begun in 1983 [6]. Paclitaxel was found to have activity against a number of solid tumors in both the refractory and de novo setting [5, 6] leading to its subsequent approval by The Food and Drug Administration in 1992 for the palliative treatment of refractory ovarian and breast cancers. Since 1993, phase III trials have shown that paclitaxel improves survival in several solid tumor disorders, including ovarian [7], non-small cell lung cancer (NSCLC) [8] and breast cancer [9].

Lung cancer remains the leading cause of cancer-related mortality in the United States [10]. Approximately 135,000 new cases of NSCLC will be diagnosed this year [11]. Although the five-year survival rate has improved over the past few decades, it currently remains at a dismal 14%. In addition to prevention strategies, the development of new chemotherapeutic agents with enhanced activity and incorporation of these agents into appropriate treatment strategies in NSCLC remain an important goal. Paclitaxel has significant single-agent activity in NSCLC and, in combination with cisplatin [12] or carboplatin [13], has been shown in randomized trials to have superior response rates [12, 13] and improved survival rates [12] compared to cisplatin/etoposide.

The purpose of this report is to review the use of paclitaxel alone in the treatment of advanced NSCLC. Studies exploring the activity of single-agent paclitaxel have used different infusion schedules as well as different dose levels. Also paclitaxel has been used both in chemotherapy-naive as well as previously treated patients. The trials will be discussed along these lines. Although it is not the intent of this paper to review the pharmacology of paclitaxel a few comments are pertinent. The pharmacokinetics of paclitaxel are complex. The clearance of paclitaxel appeared to be linear in early studies of prolonged infusions [5] but subsequent studies of shorter infusion durations suggested clearance may be non-linear [14]. Hepatic and biliary excretion have important roles in the metabolism and excretion of paclitaxel [14] while renal clearance accounts for only a small proportion of total clearance (1%-8%). Altered hepatic function clearly impacts the pharmacokinetics of paclitaxel resulting in increased myelosuppression [15], and dose reductions are necessary in these patients. Steady-state concentrations of paclitaxel do correlate with myelotoxicity [15, 16] and therefore clinical situations that may alter the pharmacokinetics of paclitaxel need to be considered.

First-Line Treatment

24-H Infusion

In 1993, two phase II trials [17, 18] appeared in the literature which utilized single-agent paclitaxel on a 24-h infusion schedule (Table 1). Murphy et al. [17] reported on 25 patients with advanced NSCLC utilizing paclitaxel at 200 mg/m² over 24 h every three weeks. The overall response rate (RR) was 22%. More impressive, the median survival was nine months with a 38% one-year survival rate. The Eastern Cooperative Oncology Group (ECOG) reported a randomized phase II trial examining merbarone and piroxantrone in addition to paclitaxel [18] in stage IV patients. Twenty-five patients were treated with paclitaxel at 250 mg/m² over 24 h every three weeks. The overall RR was 21%. The paclitaxel arm performed in a superior fashion compared to merbarone (RR = 6%) and piroxantrone (RR = 2%) with regard to survival. The one-year survival for paclitaxel was 42% versus 22% for both merbarone and piroxantrone. If one accepts the fact that merbarone and piroxantrone are inactive agents in NSCLC and that these two arms of the study are equivalent to a best supportive care arm, then this randomized phase II trial is the first to suggest that an active single-agent in NSCLC could improve survival in stage IV NSCLC. However, this cannot be definitively concluded from a randomized phase II trial. These two reports are significant in that they document single-agent activity not previously seen in advanced NSCLC.

Tan and colleagues reported on 33 patients with advanced NSCLC treated with a 24-h infusion of paclitaxel with doses ranging from 135 to 400 mg/m² [19]. The details of treatment in these patients is somewhat unclear, but they report response information in 23 patients who received at least two cycles of treatment. Five patients had partial responses (22%) and seven patients had stable disease (30%). Survival data were not reported.

These three reports [17-19] support a pooled, objective RR of approximately 22% for single-agent paclitaxel infused over 24 h. The one-year survival rate of 38%-42% is notable compared to historical experience treating metastatic NSCLC.

| Table 1. Efficacy of single-agent paclitaxel on the 24-h infusion schedule |
|-----------------------------|-----------------------------|
|                           | Murphy et al. [17] | Chang et al. [18] |
| No. pts                    | 25                      | 25                      |
| PS 0/1/2                   | 3/13/9                  | 9/15/0                  |
| % stage II/IV              | 12/88                   | 0/100                   |
| Dose (mg/m²)*              | 200                     | 250                     |
| RR (%)                     | 24                      | 21                      |
| Survival-median (mo)       | 9.3                     | 5.5                     |
| one-year (%)               | 38                      | 42                      |

* q three-week schedule
PS = performance status
RR = response rate
The major toxicity observed in these two trials was neutropenia (Table 2). Despite a 67%-80% rate of grade 3/4 leukopenia, febrile neutropenia was seen in only 8%-12% of patients. Grade 3 neuropathy was seen in approximately 20% of patients at the 200 mg/m² dose [17].

3-H Infusion

Seven phase II trials [20-26] employing a 3-h infusion schedule with single-agent paclitaxel have been reported (Table 3). Overall, 320 patients were treated in these trials, 302 of which were evaluable for response. Approximately 70% of the 320 patients had stage IV disease and 19% had a performance status of 2. The dose of paclitaxel ranged from 175 to 225 mg/m² every three weeks (six of seven trials used ≥200 mg/m²). The overall response rate was 28.5%. Median response durations were reported as 3-10 months with median survival noted as 6-11 months. One-year survival ranged from 22%-48% with a weighted one-year survival of 37.5%. The overall RR and survival rates on the 3-h infusion schedule are similar to those initially reported with the 24-h infusion schedule of single-agent paclitaxel.

The toxicity of the 3-h infusion (Table 2) of single-agent paclitaxel consisted mainly of neutropenia (≥grade 3, 2%-80%), neuropathy (≥grade 3, 0%-20%), arthralgia/myalgia (≥grade 3, 3%-24%), and nausea/vomiting (≥grade 3, 0%-8%). The incidence of hypersensitivity reactions of any grade was <2% (all studies employed standard premedications for paclitaxel administration).

A phase III study comparing paclitaxel at 200 mg/m² over 3-h to best supportive care (BSC) has recently been reported [27]. A total of 157 patients were randomized to either single-agent paclitaxel or BSC. The patients were stratified by performance status (PS) (0-1 versus 2) and stage (IIIB versus IV). The majority of patients were male (75%); 83% had ECOG PS of 0-1, and 53% had stage IV disease. The median survival for the patients treated with paclitaxel

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### Table 2. Major toxicities associated with single-agent paclitaxel*

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Neutropenia</th>
<th>Neutropenic Fever/Sepsis</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
<th>Neuropathy</th>
<th>Myalgia/Arthralgia</th>
<th>Mucositis</th>
<th>Fatigue/N/V</th>
<th>HSR</th>
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<tr>
<td>24-h infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang [18]</td>
<td>80</td>
<td>12</td>
<td>4</td>
<td>20</td>
<td>21</td>
<td>0</td>
<td>4</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Murphy [17]</td>
<td>67</td>
<td>8</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Gatzemeier [20]</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>14</td>
<td>0</td>
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<td>Alberola [21]</td>
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<td></td>
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<tr>
<td>Ranson [22]</td>
<td>34</td>
<td>14</td>
<td>0</td>
<td>5</td>
<td>19</td>
<td>24</td>
<td>0</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Millward [23]</td>
<td>32</td>
<td>4</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>0</td>
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</tr>
<tr>
<td>Furuse [24]</td>
<td>73</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>8</td>
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<tr>
<td>Tester [25]</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>NR</td>
<td>22</td>
<td>0</td>
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<tr>
<td>Sekine [26]</td>
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<td>43</td>
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<td>5</td>
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<td>3</td>
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<td>NR</td>
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<tr>
<td>1-h infusion</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hainsworth [29]</td>
<td>16</td>
<td>18</td>
<td>6</td>
<td>NR</td>
<td>4</td>
<td>11</td>
<td>NR</td>
<td>18</td>
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</tbody>
</table>

*Grade 3/4 toxicities.
N/V = nausea/vomiting; HSR = hypersensitivity reactions.

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### Table 3. Efficacy of single-agent paclitaxel on the 3-h infusion schedule

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>No. pts</td>
<td>58</td>
<td>50</td>
<td>21</td>
<td>51</td>
<td>60</td>
<td>20</td>
<td>60</td>
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<tr>
<td>PS 0-1/2</td>
<td>45/13</td>
<td>47/3</td>
<td>13/8</td>
<td>34/17</td>
<td>54/6</td>
<td>15/5</td>
<td>52/8</td>
</tr>
<tr>
<td>% stage III/IV</td>
<td>28/72</td>
<td>46/54</td>
<td>66/33</td>
<td>22/78</td>
<td>35/65</td>
<td>0/100</td>
<td>20/80</td>
</tr>
<tr>
<td>Dose (mg/m²)*</td>
<td>225</td>
<td>210</td>
<td>200</td>
<td>175</td>
<td>210</td>
<td>200</td>
<td>210</td>
</tr>
<tr>
<td>RR (%)</td>
<td>24</td>
<td>36</td>
<td>19</td>
<td>11</td>
<td>32</td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td>Survival-median (mo)</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>6.7</td>
<td>7</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>one-year (%)</td>
<td>40</td>
<td>45</td>
<td>43</td>
<td>40</td>
<td>22</td>
<td>22</td>
<td>48</td>
</tr>
</tbody>
</table>

*Three-week schedule.
was 6.8 months (95% CI = 5.7-9.1 months) compared to 4.8 months (95% CI = 3.7-6.8 months) for those patients randomized to BSC (stratified log rank, p = 0.045). The hazard ratio estimate for death was 0.70, demonstrating a 30% improvement in survival with paclitaxel as a single agent compared to BSC (Fig. 1). When survival data were compared for subsets of patients including PS (0-1 versus 2), stage (IIIB versus IV), gender, and age (>65 versus ≤65), the estimates of the relative risk of death consistently favored paclitaxel. In this study single-agent paclitaxel was associated with the following toxicity: grade 4 neutropenia 5%, grade 3/4 infection 10%, febrile neutropenia 5%, grade 3/4 peripheral neuropathy 5%, grade 3 arthralgia/myalgia 22%, grade 3/4 nausea/vomiting 5%, and grade 3/4 hypersensitivity reactions 3%. The Cancer and Leukemia Group B (CALGB 9730) is evaluating single-agent paclitaxel (225 mg/m² over 3 h) against the combination regimen of carboplatin (AUC = 6) and paclitaxel (225 mg/m² over 3 h) (Fig. 2). The rationale for this study comes from the observation that although combination regimens may improve RR, they do not clearly improve survival [28]. Since single-agent paclitaxel on both the 24- and 3-h infusion schedules has consistently been associated with a 35%-40% one-year survival rate, it is being compared to the combination of carboplatin and paclitaxel with regard to survival, quality of life, cost-utility, and cost-effectiveness. This important trial is currently ongoing in the CALGB.

1-H Infusion

Hainsworth and colleagues [29] have studied paclitaxel as a 1-h infusion in 59 patients with stage IV (n = 29) or relapsed NSCLC (n = 30). In that trial, the dose of paclitaxel varied from 135 mg/m² (n = 17) to 200 mg/m² (n = 42). Also, the infusion schedule varied from a single-day, 1-h infusion (n = 31) to a three-day, divided-dose regimen with each dose given over one hour (n = 28). A 25% RR was reported. Patients receiving the higher dose of paclitaxel (200 mg/m²) had a higher RR (31%) versus those receiving paclitaxel at 135 mg/m² (RR = 12%). Also, 6 of 16 patients (38%) previously treated with cisplatin-based regimens responded to 200 mg/m² of paclitaxel over one hour while none of 10 previously treated patients responded to 135 mg/m² of paclitaxel over one hour. The median survival of the entire group was eight months with a one-year survival rate of 33%. Toxicities were mild, with only 12% grade 3/4 leukopenia at the 200 mg/m² dose level. Grade 3 peripheral neuropathy was reported in only two patients and no grade 3/4 hypersensitivity reactions were reported.

Weekly Paclitaxel

The activity of weekly paclitaxel has been studied in both the phase I and II settings (Table 4) [30-33]. Chang et al. [30] reported on 33 patients with stage 4 NSCLC. Of note, 13 of the 33 patients had received prior treatment. The paclitaxel was given as a 1-h infusion weekly for three of four consecutive weeks. The dose of paclitaxel was escalated from 50-100 mg/m². Nineteen of the 33 patients received the phase II dose determined to be 80 mg/m² over one hour weekly for three of four consecutive weeks. A median of four cycles of treatment was given (equivalent to 12 weekly doses). The overall RR was 30% with a 4+ month median response duration. The median survival was
6.6 months with a striking 42% one-year survival. Toxicity was minimal with grade 3/4 neutropenia, reported in only 6% of patients. Nonhematologic toxicity consists of grade 2 neuropathy (3%), grade 2 myalgia/arthralgia (3%), and grade 2 diarrhea (3%).

Akerley et al. [31] have reported a phase I trial of weekly paclitaxel given over three hours for six consecutive weeks followed by a two-week rest period. The dose of paclitaxel was escalated from 100 to 200 mg/m²/week where dose-limiting neutropenia was noted. Grade 2-3 peripheral neuropathy developed in 20% of patients and occurred more commonly with greater duration of therapy. The phase II dose was 175 mg/m²/week for six consecutive weeks followed by a two-week rest period. Twenty-six patients with NSCLC were treated. A 35% overall RR was noted in the phase I setting (responses were seen at all dose levels). In a subsequent phase II trial [32], 30 patients were treated at the phase II dose. The overall RR was 56% with a one-year survival rate of 53%. The delivery of this dose-dense regimen was difficult over time. Only 58% and 50% of the intended doses were deliverable during cycles 3 and 4, respectively. This was mainly due to grade 3/4 neutropenia and grade 2/3 peripheral neuropathy.

The CALGB has studied weekly paclitaxel in advanced NSCLC [33]. The dose in this study (CALGB 9731) was reduced to 150 mg/m²/week for six consecutive weeks followed by a two-week rest period. Thirty-six evaluable patients were treated. Toxicity consisted of grade 3/4 hematologic toxicity in 33% (mainly neutropenia), grade 3 neutropenia in 28% and grade 3 hyperglycemia in 32%. There were 14 partial responses for an overall RR of 39%. No mature survival data are yet available from this trial. These cooperative group data confirm the previous phase II data and show that this dose-dense regimen of weekly paclitaxel may be administered safely, yielding RR and preliminary survival data comparable to combination regimens.

### Second-Line Treatment

Paclitaxel has been studied as second-line therapy in breast and ovarian cancers and shown to be active when administered on alternative schedules. Seidman et al. [34] administered a 96-h infusion of paclitaxel (120-140 mg/m²) to 26 patients with metastatic breast cancer who progressed on short-infusion taxane therapy. A 27% response rate was reported. Fennelly et al. [35] investigated the administration of weekly paclitaxel in 18 extensively taxane pre-treated patients with relapsed ovarian cancer. A 31% response rate was reported. These trials suggest that altered schedules of paclitaxel may overcome resistance to more traditional schedules or may exert their effect by alternative mechanisms of action. These issues have not yet been clearly defined.

Several investigators have examined the activity of paclitaxel as second-line therapy in NSCLC (Table 5). The characteristics of patients treated with regard to prior therapy, previous response, and disease-free interval status are not always clearly reported. Murphy et al. [36] reported on 40 patients who had failed platinum-containing regimens and were treated with 24-h paclitaxel at 175–200 mg/m². Approximately 33% of the patients were PS 2. One partial response (RR = 3%) and two marginal responses were observed. Six patients experienced brief stabilization of their disease. The remainder of the patients suffered progressive disease. Survival data were not reported. Ruckdeschel et al. [37] reported on 14 patients who had failed platinum-containing regimens. Six had a performance status of 2. Paclitaxel was given at 200-250 mg/m² over 24 h. Two patients (14%) had partial responses and two had prolonged stabilization of disease. The median survival was four months, but five patients were alive 6+ and 11+ months later. The major toxicity was profound fatigue, which was dose-limiting. Hainsworth et al. [29] reported on a 1-h infusion of paclitaxel in 26 patients with NSCLC previously treated with cisplatin-based regimens.

<table>
<thead>
<tr>
<th>Table 4. Single-agent paclitaxel-weekly infusions</th>
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</thead>
<tbody>
<tr>
<td><strong>Chang et al. [30]</strong></td>
</tr>
<tr>
<td>No. pts</td>
</tr>
<tr>
<td>PS 0-1/2</td>
</tr>
<tr>
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</tr>
<tr>
<td>Dose (mg/m²)</td>
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<tr>
<td>RR (%)</td>
</tr>
<tr>
<td>Survival-median(mo.)</td>
</tr>
<tr>
<td>-one-year(%)</td>
</tr>
</tbody>
</table>

*Ph I-weekly for three of four wks-1-h infusion-maximum tolerated dose (MTD) = 80 mg/m².
**Ph I-weekly for six of eight wks-3-h infusion-MTD = 175 mg/m².
†Ph II-weekly for six of eight wks-3-h infusion.
‡Ph II-weekly for six of eight wks-3-h infusion.
NS = not stated; TE = too early.
Two dose levels were studied (135 and 200 mg/m\(^2\)). No responses were observed in the 10 patients previously treated with paclitaxel at 135 mg/m\(^2\) over one hour. In the 16 patients treated with paclitaxel at 200 mg/m\(^2\) over one hour, the response rate was 38%. This overall 23% RR on the one-hour schedule is encouraging and worthy of further study. In another study [38] employing an every three- to four-week schedule, 16 patients with refractory NSCLC who had progressed during or after prior platinum-based therapy were treated with paclitaxel at 130-175 mg/m\(^2\). The infusion time was not reported. Although no response data were reported, an overall median survival of 10 months and a one-year survival of 45% were reported.

Weekly paclitaxel has also been studied by Chang and his colleagues [30]. Thirteen previously treated patients were entered in this phase I/II trial and received doses ranging from 50-100 mg/m\(^2\) over one hour weekly for three of four weeks. These patients were included with 20 other patients receiving weekly paclitaxel as first-line treatment. The second-line patients were not reported on separately, but the overall experience was notable for an RR of 30% and a 42% one-year survival.

In preclinical studies there was a suggestion that paclitaxel exhibited schedule-dependent activity [39]. Because of this, the 96-h infusion schedule (140 mg/m\(^2\) every three weeks) was investigated in 13 patients undergoing refractory to platinum-based or short-infusion (24-h) paclitaxel-based regimens [40]. No objective responses were reported, but disease stabilization was seen in 23% of patients. Chang et al. [41] reported on 10 patients with refractory NSCLC failing first-line treatment with cisplatin-containing regimens. All 10 were treated with a 3-h infusion (mg/m\(^2\)) with only one partial response. Six patients who progressed on the 3-h infusion were treated with 96-h infusional paclitaxel at 135 mg/m\(^2\); no responses were seen. This experience suggesting the preclinical observation that prolonged infusions of paclitaxel enhance cytotoxicity [39] does not translate into a clinical advantage in the refractory setting.

The role of second-line therapy in NSCLC remains controversial. It is unclear how many patients failing first-line therapy are candidates for further cytotoxic therapy because of declining performance status at the time of progression. Characteristics of patients that might predict a benefit from second-line treatment are not always reported. These characteristics may include performance status, response to initial therapy, duration of response or progression-free interval, and time since previous treatment, as well as others. In a phase III trial currently ongoing at the University of North Carolina, weekly administration of paclitaxel is being evaluated as second-line treatment (Fig. 3). This trial is attempting to address the optimal duration of first-line treatment.
with advanced or metastatic NSCLC are randomized to either four cycles of carboplatin/paclitaxel or continuous carboplatin/paclitaxel until objective progression. In both arms, weekly paclitaxel at 80 mg/m² is administered at the time of progression. Patients who progress after the initial two cycles of treatment (first response evaluation), those who receive four cycles and then have a “treatment-free” interval prior to progression, and those patients who receive continuous treatment and progress will be evaluated separately with regard to their response to weekly paclitaxel. These data will be helpful in defining which patients may benefit most from second-line weekly paclitaxel in refractory NSCLC.

In summary, there is a paucity of data for single-agent paclitaxel in refractory NSCLC. Given the promising results of some of these studies, future studies should, in our opinion, be done [28, 38]. The characteristics of the patients participating in these studies should be well-described, and studies should be designed to assess the impact of single-agent paclitaxel on appropriate outcomes such as survival, symptom-relief and overall quality of life in this setting.

**CONCLUSION**

Single-agent paclitaxel has substantial activity in advanced NSCLC as judged by RR and its impact on survival in both the phase II and III settings. This has been shown on all infusion schedules studied thus far, including 24-, 3-, and 1-h infusions as well as weekly schedules. The optimal schedule has not yet been defined, nor has the optimal dose. Despite the lack of randomized phase III trials addressing the issues of dose and schedule in NSCLC, the phase II trials completed to date suggest that, when considering clinical outcomes (response rate and survival), all schedules appear active. Although a dose-response effect on survival was not apparent in a large phase III trial when paclitaxel (24-h infusion) was combined with cisplatin [8], the impact of dose has not been studied extensively with the shorter infusion schedules either alone or in combination with the platinums. The work of Hainsworth et al. [29] indirectly suggests that dose is important, as the RR at 200 mg/m² was superior to the RR at 135 mg/m² on a 1-h infusion schedule. However, this was not a randomized trial. In a study of 3-h paclitaxel infusions in combination with carboplatin, a dose of 225 mg/m² appeared superior to 175 mg/m² in the phase III setting [42]. These studies suggest a dose-threshold effect at least for the shorter infusion schedules with optimal doses being ≥200 mg/m².

The weekly infusion schedules also appear very promising in the phase II setting. Paclitaxel can be delivered with acceptable toxicity in a dose-dense fashion achieving at least a twofold dose intensity. The preliminary results suggest this schedule is very active and certainly worthy of further study.

The data presented in this report suggest that single-agent paclitaxel has activity comparable to many combination regimens. Given this, it is appropriate to compare single-agent paclitaxel to combination regimens as the CALGB is doing (Fig. 2). Likewise, paclitaxel is an attractive agent to combine with other new active agents in an effort to increase the overall efficacy of therapy in advanced NSCLC. The European Organization for the Research and Treatment of Cancer is currently conducting a randomized phase III trial in which one of the arms is paclitaxel in combination with gemcitabine. Future studies will undoubtedly compare other combinations either with or without the platinums.

Finally, moving forward in the treatment of NSCLC, novel therapies must be studied in a rigorous fashion. In advanced metastatic disease where palliation is the goal, a balance between activity, toxicity, and quality of life must be achieved. When active agents or regimens are identified, they should be integrated into earlier stages of the disease in combination with the two local modalities of surgery and thoracic radiation therapy where the goal is often cure. The activity of single-agent paclitaxel in NSCLC deserves further study, particularly novel approaches such as dose-dense weekly paclitaxel. Its use should be studied with the appropriate endpoints in mind, which will be dictated by the stage of disease being treated.

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