Considerations for Second-Line Therapy of Non-Small Cell Lung Cancer

THOMAS E. STINCHCOMBE, MARK A. SOCINSKI

Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Key Words. Pemetrexed • Erlotinib • Docetaxel • Chemotherapy • Treatment selection

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Abstract

For patients with advanced non-small cell lung cancer and a good functional status, platinum-based first-line chemotherapy improves quality of life, reduces disease-related symptoms, and improves survival. The addition of bevacizumab to carboplatin and paclitaxel in the first-line setting has been shown to produce a higher response rate and longer progression-free survival and overall survival times than with carboplatin and paclitaxel. Despite these therapies, all patients inevitably experience disease progression. There are currently three agents approved for treating patients who progress after one prior regimen: docetaxel, pemetrexed, and erlotinib. Erlotinib is also indicated for patients who progress after two prior regimens. These agents appear to have similar efficacies in terms of response and overall survival, but have significantly different toxicity profiles. Currently, the choice of agent depends on a number of factors, including the patient’s comorbidities, toxicity from previous treatments, the risk for neutropenia, smoking history, and patient preference. A better understanding of prognostic factors in the second-line setting may allow clinicians to better select patients for second-line therapy, and lead to better-designed second-line trials. Patients with a good performance status in second-line trials have a median survival duration of approximately 9 months, and may receive two second-line therapies during the course of their treatment. Several new agents have shown activity in phase II trials, and may be integrated into second-line therapy as single agents or in combination with current agents in the future. The Oncologist 2008;13(suppl 1):28–36

Introduction

Lung cancer is the leading cause of cancer-related mortality in the U.S., and it is estimated that, in 2007, more patients will die of lung cancer than of breast, colon, and prostate cancer combined [1]. For approximately two thirds of non-small cell lung cancer (NSCLC) patients who present with advanced-stage disease, generally defined as stage IIIIB or stage IV disease, the primary treatment is chemotherapy [2]. In addition to patients who present with advanced-stage disease, a significant percentage of patients who present with local or locoregional disease will relapse with metastatic disease. For patients who have a good performance status and are fit to receive chemotherapy, the standard therapy is platinum-based chemotherapy. While these drugs improve the quality of life, reduce symptoms, and prolong survival, patients eventually experience disease progression. Currently, the choices of second-line therapy are limited to those shown to prolong survival in phase III trials. However, several new agents have shown activity in phase II trials, and may be integrated into second-line therapy in the future. The Oncologist 2008;13(suppl 1):28–36

status (PS), chemotherapy has been shown to produce longer survival, palliate disease-related symptoms, and produce a better quality of life than with best supportive care (BSC) [3]. Many patients benefit from initial treatment with chemotherapy, although all patients eventually experience disease progression, generally within a median of 3–6 months of initiating chemotherapy [4, 5]. While it is difficult to estimate the proportion of patients who receive second-line treatment, approximately 40%–50% of patients did so in recent first-line trials [5, 6]. Patients who appear more likely to receive second-line therapy are those with a good PS, female patients, and those with nonsquamous histology [7]. Many patients who maintain a good PS and tolerate therapy without significant toxicities will receive third-line therapy. In a recent phase III trial of second-line therapies, approximately 40% of the patients subsequently received third-line therapy [8]. The characteristics of this patient population have not been well studied.

**Current Second-Line Treatment Options**

Three agents are currently approved by the U.S. Food and Drug Administration (FDA) in the second-line setting: two cytotoxic chemotherapy agents, docetaxel (Taxotere®; Sanofi-Aventis, Bridgewater, NJ) and pemetrexed (Alimta®; Eli Lilly and Company, Indianapolis, IN), and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib (Tarceva®; Genentech, Inc., South San Francisco, CA and OSI Pharmaceuticals, Melville, NY) [9–12]. These agents were approved based on four phase III trials, and there was some variation among patient characteristics included in the trials (Table 1). Erlotinib is also approved for use in the third-line setting.

Docetaxel was the first agent approved by the FDA for second-line therapy based on two phase III trials (Table 2). The TAX 317 trial initially compared docetaxel at a dose of 100 mg/m² every 3 weeks with BSC; however, after five treatment-related deaths the trial was amended and the dose of docetaxel was reduced to 75 mg/m² [10]. That trial revealed a longer time to progression, longer median survival time, and greater 1-year survival rate with docetaxel (75 mg/m²) over BSC. The TAX 320 trial compared docetaxel at 100 mg/m², docetaxel at 75 mg/m², and a control arm of either vinorelbine (30 mg/m²) on days 1, 8, and 15 or ifosfamide (2 mg/m² per day) on days 1–3 every 3 weeks [12]. While the overall survival was not different among the three treatment groups, the 1-year survival rate was significantly higher with docetaxel at 75 mg/m² than with the controls. These trials established docetaxel at a dose of 75 mg/m² every 3 weeks as the standard therapy in the second-line setting.

Pemetrexed, a multitargeted antifolate compound, was approved in the second-line setting based on a phase III noninferiority trial [11]. The major target of pemetrexed is the enzyme thymidylate synthase, and other targets include glycaminide ribonucleotide formyl transferase and dihydrofolate reductase [13]. These enzymes are critical for the synthesis of purine nucleotides and thymidine. The initial trials with pemetrexed revealed high rates of myelosuppression, mucositis, and diarrhea [14]. Previous trials with antifolate agents revealed that vitamin supplementation could reduce the incidences of mucositis and myelosuppression [15]. To investigate whether a patient’s folate status impacted the toxicity of pemetrexed, pretreatment blood samples collected from patients treated in phase I and II trials between 1995 and 1999 were assayed for evidence of folate, B₁₂, and B₆ deficiency. A multivariate analysis performed on data from 246 patients revealed that baseline homocysteine and methylmalonic acid levels were predictive of hematologic and nonhematologic toxicities [16]. Elevated homocysteine levels correlated with the incidence of grade 3 or 4 thrombocytopenia and neutropenia with and without associated grade 3 or 4 diarrhea and mucositis, and elevated methylmalonic acid levels independently correlated with the incidence of grade 3 or 4 mucositis and diarrhea. Patients with elevated levels of both homocysteine and methylmalonic acid were found to be at high risk for severe toxicity. This analysis was unable to establish a threshold level at which the risk for toxicity was sufficiently

**Table 1.** Patient characteristics of select phase III trials in the second-line treatment of non-small cell lung cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Performance status score 0/1 (%)</th>
<th>n of prior regimens (%)</th>
<th>Best previous response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 317 [10]</td>
<td>204</td>
<td>76</td>
<td>74, 26</td>
<td>34, 35, 19</td>
</tr>
<tr>
<td>TAX 320 [12]</td>
<td>373</td>
<td>83</td>
<td>70, 30</td>
<td>71a, 29</td>
</tr>
<tr>
<td>BR.21 [9]</td>
<td>731</td>
<td>66</td>
<td>50, 50</td>
<td>40, 39, 21</td>
</tr>
</tbody>
</table>

*Previous response reported as response/stable versus progressive disease. Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.*

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low that vitamin supplementation was not necessary. Thus, all patients treated with pemetrexed required supplementation with vitamin B₁₂ (1,000 μg i.m. every 9 weeks) and folic acid (350–1,000 μg orally daily).

As a result of finding a relationship between homocysteine and methylmalonic acid levels, an ongoing phase III trial of cisplatin plus pemetrexed versus cisplatin alone in malignant pleural mesothelioma was amended [17]. Beginning in December 1999, folic acid and vitamin B₁₂ supplementation was required for all patients receiving pemetrexed and for those subsequently enrolled in the trial. The amendment resulted in three different subgroups of patients: never supplemented patients (NSP) (n = 32), partially supplemented patients (PSP) (n = 26), and fully supplemented patients (FSP) (n = 168). The incidence of grade 3 or 4 neutropenia was significantly higher in the NSP and PSP patients than in the FSP patients (41.4% versus 23.3%, respectively; p = .011). The FSP and PSP groups of patients, in comparison with the NSP group, had a statistically significant lower incidence of nausea, vomiting, and febrile neutropenia. The median survival time in the FSP and PSP groups was longer for the pemetrexed plus cisplatin arm than for the cisplatin alone arm (13.2 versus 9.4 months, respectively; hazard ratio [HR], 0.71; p = .022). Thus, the subgroup analysis indicated that the addition of vitamin supplementation reduced toxicity without adversely affecting the efficacy of the pemetrexed-containing treatment arm.

Based on the results of phase II trials of single-agent pemetrexed [18, 19], single-agent pemetrexed (500 mg/m² every 3 weeks) with vitamin supplementation was compared with standard-dose docetaxel every 3 weeks in a phase III clinical trial in advanced NSCLC [11]. That trial differed from the other second-line trials in that patients were only allowed to have received one previous line of treatment for advanced disease. It was originally designed to test for the superiority of pemetrexed, but the trial was amended and a noninferiority trial design was adopted. This trial did not reach the statistical endpoint of noninferiority of survival for pemetrexed according to the fixed margin method, but using the percent retention method, results were adequate to define noninferiority. Pemetrexed did demonstrate clinical efficacy similar to that of docetaxel. In order to determine noninferiority for survival, the survival effect of docetaxel has to be reliably determined over multiple studies in order to evaluate for interstudy variability [20]. The TAX 317 trial revealed a survival benefit for the 55 patients treated with docetaxel (75 mg/m²) over BSC [10]. The TAX 320 trial did not reveal a difference in overall survival between the two treatment arms, but did reveal a difference in the 1-year survival rates [12]. Thus, there were limited historical data to help estimate the survival effect of docetaxel. Further complicating the survival analysis was the fact that 32% of the pemetrexed-treated patients received docetaxel after disease progression [11]. The other efficacy parameters, response rate and progression-free survival, were similar between the two treatment arms and suggested that the clinical benefits from pemetrexed and docetaxel would be similar [20]. Pemetrexed had a significantly lower rate of hematologic toxicity, including a lower rate of febrile neutropenia and a similar rate of grade 3 or 4 nonhematologic toxicities (Table 3). Based on these factors, the FDA approved pemetrexed for the second-line treatment of NSCLC.

A Cox proportional multiple regression analysis found that a good PS score (0–1 versus 2), disease stage (III versus IV), and longer time since first-line chemotherapy (≥3

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>Median n of cycles</th>
<th>Response rate (%)</th>
<th>Median survival time (months)</th>
<th>1-Year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 317 [10]</td>
<td>D100</td>
<td>2</td>
<td>7.1</td>
<td>5.9</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>D75</td>
<td>4</td>
<td>7.1</td>
<td>7.5</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>–</td>
<td>–</td>
<td>4.6</td>
<td>11</td>
</tr>
<tr>
<td>TAX 320 [12]</td>
<td>D100</td>
<td>3</td>
<td>10.8</td>
<td>5.5</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>D75</td>
<td>3</td>
<td>6.7</td>
<td>5.7</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>V/I</td>
<td>3/2</td>
<td>0.8</td>
<td>5.6</td>
<td>19</td>
</tr>
<tr>
<td>JMEI, Hanna et al. [11]</td>
<td>D75</td>
<td>4</td>
<td>8.8</td>
<td>7.9</td>
<td>29.7</td>
</tr>
<tr>
<td></td>
<td>Pem</td>
<td>4</td>
<td>9.1</td>
<td>8.3</td>
<td>29.7</td>
</tr>
<tr>
<td>BR.21 [9]</td>
<td>E150</td>
<td>–³</td>
<td>8.9</td>
<td>6.7</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>–</td>
<td>–</td>
<td>4.7</td>
<td>21</td>
</tr>
</tbody>
</table>

³Erlotinib was given until disease progression or unacceptable toxicity.

Abbreviations: BSC, best supportive care; D100, docetaxel 100 mg/m² every 3 weeks; D75, docetaxel 75 mg/m² every 3 weeks; E150, erlotinib 150 mg daily; Pem, pemetrexed 500 mg/m² every 3 weeks; V/I, vinorelbine or ifosfamide.
months versus <3 months) were associated with longer survival after second-line chemotherapy [11]. The median survival time for patients with a PS score of 0 or 1 was 9 months in both treatment arms. A subset analysis of elderly patients (≥70 years old) in that trial revealed no significant difference in median survival time between elderly and younger patients [21]. Elderly patients treated with pemetrexed had a survival time similar to that of elderly patients treated with docetaxel; however, the rate of febrile neutropenia was significantly lower in elderly patients treated with pemetrexed than in those treated with docetaxel (2.5% versus 19%, respectively; \( p = .025 \)).

The National Cancer Institute of Canada BR.21 trial compared erlotinib, an oral EGFR TKI, with BSC in 731 patients with advanced NSCLC. Patients were required to have received one or two regimens of combination chemotherapy and not be eligible for further chemotherapy [9]. That trial revealed statistically significant higher progression-free and overall survival rates with erlotinib treatment (Table 2). Erlotinib was well tolerated; the principal toxicities were rash and diarrhea. An exploratory univariate analysis demonstrated that the survival benefit with erlotinib therapy was similar across multiple subgroups [9]. A separate analysis revealed that smoking status appeared to be the most powerful predictor of a survival effect with erlotinib: never-smokers (defined as <100 cigarettes in an entire lifetime) receiving erlotinib had a significantly higher survival rate than patients in the placebo arm (HR, 0.4; \( p < .01 \)) [22]. A separate analysis performed by Florescu et al. [23] attempted to identify the patient characteristics that are predictive of early progression (defined as within 8 weeks) and early death (defined as within 3 months). Using stratification factors and potential prognostic factors, the Cox regression analysis suggested that factors associated with early death (survival time of <3 months) were: a PS score of 2–3 (\( p < .0001 \)), weight loss of >5% (\( p < .0001 \)), anemia (defined as a hemoglobin level below normal limits; \( p < .0001 \)), progressive disease on prior therapy (\( p < .0001 \)), non-Asian ethnicity (\( p = .008 \)), a high lactate dehydrogenase (LDH) level (\( p < .0001 \)), and a time from diagnosis to randomization of <12 months (\( p = .0003 \)) [23].

The response rates reported with all three agents in these trials were 7%–11%, the median survival times were 6–8 months, and the 1-year survival rates were approximately 30%. While the median survival time seen in the BR.21 study was numerically lower than that in the TAX 317 and JMEI (phase III study of pemetrexed versus docetaxel; Hanna et al. [11]) trials, BR.21 included patients with a PS score of 3 and a higher percentage of patients with two or more previous therapies; therefore, variations in patient populations may have contributed to this difference. While efficacy appears to be similar with all three agents, there are significant differences in the toxicity profiles (Table 3). Docetaxel has a significantly higher rate of hematologic toxicities than pemetrexed and erlotinib, which has no significant hematologic toxicity. Pemetrexed and docetaxel have a similar rate of nonhematologic toxicities, while erlotinib appears to have a higher rate, predominantly manifesting as rash and diarrhea.

### Prognostic Factors

While the prognostic factors associated with improved survival with first-line therapy have been extensively studied, less information exists about the prognostic factors in second-line therapy. For the treating physician, prognostic factors may assist in determining the likelihood of clinical benefit of further therapy. Bonomi et al. [24] recently reported the prognostic factors in a second-line trial that compared docetaxel with paclitaxel poliglumex (PPX) in 849 patients [24]. There was no difference in survival between the two treatment arms. The following factors were associated with shorter survival: an Eastern Cooperative Oncology Group PS score of 2 versus 0–1 (HR, 2.19; \( p < .001 \)), a hemoglobin level of <11 g/dl versus ≥11 g/dl (HR, 1.78; \( p < .001 \)), an LDH level of <200 U/l versus ≥200 U/l (HR, 1.72; \( p < .001 \)), a lung cancer symptom score of <18 versus ≥18 (HR, 1.47; \( p < .001 \)), male gender (HR, 1.39; \( p = .005 \)), extrathoracic metastases (HR, 1.45; \( p < .001 \)), prior radiation therapy (HR, 1.40; \( p = .001 \)), and starting second-line chemotherapy <4 months after the start of first-line chemotherapy (HR, 1.37; \( p = .003 \)). A recent analysis by Weiss et al. [25] retrospec-

### Table 3. Selected grade 3 or 4 toxicities with second-line agents [9, 11]

<table>
<thead>
<tr>
<th></th>
<th>Pemetrexed (% patients)</th>
<th>Docetaxel (% patients)</th>
<th>Erlotinib (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.3</td>
<td>5.4</td>
<td>19</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.6</td>
<td>1.8</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.5</td>
<td>1.1</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.4</td>
<td>2.5</td>
<td>6</td>
</tr>
<tr>
<td>Neurosensory</td>
<td>0</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>0.8</td>
<td>0.7</td>
<td>9</td>
</tr>
<tr>
<td>Alopecia*</td>
<td>6.4</td>
<td>37.7</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5.3</td>
<td>40.2</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>4.2</td>
<td>4.3</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.9</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.9</td>
<td>12.7</td>
<td>0</td>
</tr>
</tbody>
</table>

*Any grade.
tively reviewed the impact of first-line chemotherapy on outcome of second-line chemotherapy in patients included in the JMEI (Hanna et al. [11]) trial. On multivariate analysis, gender, stage at diagnosis, PS, and best response to first-line therapy significantly influenced overall survival [25]. The time elapsed since first-line therapy was a significant prognostic factor on univariate analysis, but not on multivariate analysis.

A better definition of prognostic factors in the second-line setting will be important when interpreting the outcomes of future phase II and III trials. This may be particularly relevant when attempting to assess the efficacy of a new agent in a phase II trial of second-line therapies. Future phase III trials may have to be designed to stratify for specific prognostic factors between the two treatment arms. A better understanding of prognostic factors would also assist in the optimal selection of patients for second-line trials. Patients with a marginal or poor PS appear to derive limited benefit from current second-line therapies; clinical trials specifically designed for this population may be developed in the future.

**Factors in Selecting Second-Line Therapy**

**Patient Preference**

Docetaxel, pemetrexed, and erlotinib have significantly changed the treatment paradigm for advanced NSCLC; however, the optimal integration of first- and second-line therapies is yet to be defined. At this time, the selection of a second-line agent may depend on a number of factors, including physician preference, patient preference, patient comorbidities, and smoking history. The response, time to tumor progression, and toxicities related to first-line therapies may also have a role in the selection of a second-line agent. Given the incurable nature of advanced NSCLC, and the modest survival seen in the second-line setting, patient convenience and preference should be considered when selecting a second-line agent. In order to assess patient preferences, Dubey et al. [26] performed a survey of 464 lung cancer patients registered in the Alliance for Lung Cancer Advocacy, Support, and Education about their treatment preferences and concerns about toxicity [26]. In that survey, 73% of respondents reported that, if given the option, they would choose a chemotherapy regimen because of the side-effect profile, assuming that the outcome was equivalent. The remaining respondents stated that the side effects were not important when choosing a chemotherapy regimen, or they were unsure whether side effects would influence their decision. The side effect that was considered most important when selecting chemotherapy was nausea/vomiting (48%), followed by a risk for infection (20%), fatigue (13%), hair loss (9%), other (5%), and numbness/tingling (4%). Patients with a history of prior chemotherapy treatment were more likely to be concerned about alopecia and the risk for infection than chemotherapy-naïve patients. Hair loss was a common concern in both men and women (84%), but it was only important enough to affect the choice of chemotherapy in 4% of men and 11% of women. Patients with dependent children at home were more likely to be worried about alopecia, fatigue, and numbness/tingling than were patients who did not have children. Only 25% of respondents reported having discussed with their physician the possibility of choosing a chemotherapy regimen based on the toxicity profile.

Erlotinib is an oral agent, which some patients may prefer, and it may be associated with fewer visits to the physician’s office for treatment. This could be more convenient for patients with a marginal functional status, who have transportation difficulties, or who live a significant distance from the physician’s office. Erlotinib should be taken daily 1 hour before or 2 hours after food, and thus requires patient compliance with the regimen. Some patients may have cosmetic concerns about the potential for rash, and patient education about rash should be given and discussed prior to initiating treatment. Supportive care guidelines for the management of rash are available [27]. A light or never-smoking history has been associated with a high rate of response to erlotinib, and this may be the preferred agent in that patient population.

Both docetaxel and pemetrexed require premedication with steroids, and some patients tolerate steroid premedication poorly, with complications such as hyperglycemia and insomnia. If a patient is intolerant of steroids then erlotinib may be the preferred agent. Docetaxel has a higher rate of sensory neuropathy than pemetrexed or erlotinib, and patients who have a hobby or occupation that requires finger or hand dexterity may prefer to avoid this potential complication. Pemetrexed and erlotinib have low rates of alopecia (6.4% and 0%, respectively), and so patients who wish to avoid alopecia may prefer one of those two agents [9, 11].

**Patient Comorbidities**

In addition to patient preference, a patient’s comorbidities may impact the selection of second-line therapies. A significant percentage of patients with advanced NSCLC will have some degree of renal insufficiency. Pemetrexed is contraindicated in patients with a glomerular filtration rate of <40 ml/minute, and patients with impaired renal function have been shown to have greater drug exposure [28]. Because nonsteroidal anti-inflammatory drugs (NSAIDs) are known to suppress antifolate renal tubular secretion, patients should discontinue NSAIDs 2–5 days before pemetrexed adminis-
lation [29]. While erlotinib is metabolized by the liver, and renal excretion accounts for approximately 9% of the administered dose, case reports indicate that erlotinib can safely be given to patients with renal failure [30]. Docetaxel is metabolized by the liver and renal excretion is minimal (<5%), and so it may be given to patients with renal insufficiency, but dose adjustments are required for those with hepatic impairment [31]. Docetaxel has a higher rate of sensory neuropathy than pemetrexed and erlotinib, and so the latter two agents may be preferable in patients with diabetic neuropathy or residual neuropathy from first-line therapy [11].

Methotrexate, which has a chemical structure similar to that of pemetrexed, is contraindicated in patients with uncontrolled pleural effusions or ascites because of accumulation of methotrexate in these third space fluids. Currently, the effect of third space fluid on pemetrexed pharmacokinetics is unknown, and draining the effusion prior to pemetrexed treatment should be considered. Pharmacokinetic studies on a patient who developed acute renal failure and ascites after treatment with cisplatin and pemetrexed found persistent pemetrexed levels in the ascitic fluid and plasma [32]. The schedule of pemetrexed daily for five consecutive days was found to have significant toxicity, suggesting that prolonged exposure to the drug may increase toxicity [33]. Until trials investigating the influence of pleural effusions on the pharmacokinetics and toxicity of pemetrexed are completed, pemetrexed should not be used in patients with clinically significant, uncontrolled pleural effusions or ascites. Our practice has been to treat pleural effusions that are only detectable on computed tomography scans as not clinically significant.

**Risk for Neutropenia**

Febrile neutropenia is a major and potentially life-threatening complication of chemotherapy. Commonly cited risk factors for developing febrile neutropenia include poor PS, advanced-stage disease, elderly age (≥65 years), and prior chemotherapy [34, 35]. A higher incidence of febrile neutropenia in the first treatment cycle than in subsequent cycles has been reported in several trials [36–38]. The reasons for this are unclear, but the observation indicates that preventive strategies should be implemented prior to the first cycle. Potential strategies for reducing the possibility of febrile neutropenia include selecting a chemotherapy regimen with a low rate of neutropenia, the use of prophylactic growth factors, and the use of prophylactic antibiotics [34, 36, 39]. Of the agents approved for second-line therapy, erlotinib and pemetrexed have low rates of febrile neutropenia, and these agents may be preferred if a patient is thought to be at high risk for developing febrile neutropenia or has had significant myelosuppression with first-line therapy.

One strategy to reduce the rate of myelosuppression is treatment with weekly docetaxel, and this has been investigated in several phase II and III trials using various schedules and doses (Table 4). In general, these trials have shown equivalent response rates and survival times across the weekly and 3-weekly regimens [40–44]. The rates of nonhematologic toxicities such as mucositis, diarrhea, and dyspnea were not lower with weekly docetaxel, and were in fact higher in some trials [40, 42]. Two trials revealed a lower rate of febrile neutropenia [41, 42], and most reported a lower rate of grade 3 or 4 neutropenia. A recent meta-analysis of individual patient data from five trials comparing weekly docetaxel with every-3-weeks docetaxel revealed similar median survival times (27.4 weeks versus 26.1 weeks, respectively; \( p = .24 \)) [45]. In comparison with weekly docetaxel, the 3-weekly regimen produced significantly more febrile neutropenia (6% versus <1%, respectively; \( p < 0.00001 \)). No significant differences in toxicity between the two schedules were observed for anemia, thrombocytopenia, and nonhematologic toxicities. These trials and the meta-analysis indicate that weekly docetaxel may be an acceptable alternative, although the lack of a difference in efficacy, the more frequent use of steroids, the inconvenience of weekly administration, and the availability of other equally effective agents with low rates of myelosuppression argue against the routine use of this treatment schedule.

**Gefitinib**

Gefitinib (Iressa®; AstraZeneca, Wilmington, DE) was approved by the FDA in May 2003 with an accelerated approval procedure for third-line therapy on the basis of two phase II trials [46, 47]. However, a subsequent phase III trial \( n = 1,692 \) did not reveal a statistically significant difference in overall survival for treatment with gefitinib versus BSC in patients who had progressed after one or two previous chemotherapy treatments [48]. In June 2005, the FDA restricted the use of gefitinib to patients who were participating in currently open clinical trials or continuing to benefit from treatment. While gefitinib was not a treatment option for the vast majority of the patients in the U.S. it was approved in other countries, and trials investigating the activity of gefitinib continued. A recent phase III trial compared the efficacy of docetaxel (75 mg/m² every 3 weeks) with that of gefitinib (250 mg daily) in patients who had progressed after chemotherapy \( n = 1,466 \) [49]. The primary endpoint was the noninferiority of gefitinib in comparison with docetaxel in terms of overall survival, and the coprimary endpoint was the superiority of gefitinib in patients with high EGFR gene copy number. Approximately 20% of patients were of
Asian ethnicity and never-smokers, and adenocarcinoma was the most frequent histology, approximately 55% in both arms. The overall survival times were similar in the two treatment arms (HR, 1.020; 96% confidence interval [CI], 0.905–1.150), demonstrating noninferiority for gefitinib relative to docetaxel. In the subset of patients with high \( \text{EGFR} \) gene copy number (\( n = 174 \)), the overall survival times were similar (HR, 1.09; 95% CI, 0.78–1.51; \( p = .6199 \)); thus, there was no demonstrated statistical superiority of gefitinib in comparison with docetaxel in this subset. In a preplanned subset analysis in patients who were never-smokers, of Asian ethnicity, and with adenocarcinoma histology, no statistically significant difference in overall survival was observed between the two treatment arms. More patients treated with gefitinib experienced a statistically significant and clinically relevant improvement in quality of life compared with those treated with docetaxel, and the rate of overall adverse events and the treatment-related adverse events were numerically lower in the gefitinib arm. While the results of that trial are provocative, it is unknown if the regulatory status of gefitinib in the U.S. will change. The results of the subset analysis in patients with high \( \text{EGFR} \) gene copy number may influence current and future trials investigating biomarkers.

### CONCLUSIONS

The development of several agents with efficacy in the second-line treatment of NSCLC has been a significant advance. Given the similar efficacies of the three currently available agents, patient preference, comorbidities, and convenience are important issues to consider when selecting a therapeutic agent. Recent trials with PPX and oral topotecan have shown efficacy similar to that of standard therapy [50, 51]. Several new agents, such as vinflunine, cetuximab, sunitinib, sorafenib, and vandetanib, have shown significant activity in the second-line setting in phase II trials [52–55]. These agents alone or in combination may increase the efficacy over that seen with current second-line therapies. A recent, randomized, phase II trial that investigated bevacizumab in combination with chemotherapy (pemetrexed or docetaxel) or erlotinib versus chemotherapy alone revealed a trend toward a lower progression-free survival rate in the bevacizumab arms [56]. Hopefully, as the data on second-line therapies mature, strategies for selecting the optimal treatment for an individual patient based on clinical factors (e.g., smoking history), molecular characteristics, and response to and toxicity of first-line therapy will be developed. The development of new therapeutic options for patients with a poor PS or who progress rapidly after first-line therapy is an area of active investigation.

### REFERENCES


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