Consequences of targeted treatments for second-line therapy

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The paradigm for first-line treatment of relapsed or metastatic non-small cell lung cancer (NSCLC) is changing. Large phase III trials demonstrated that, in 2010, we cannot select a therapy without an accurate definition of tumor histology and epidermal growth factor receptor (EGFR) status. Patients harboring an EGFR-activating mutation have a better prognosis and certainly are extremely sensitive to EGFR-tyrosine kinase inhibitors, while other agents, such as bevacizumab or pemetrexed, are more effective and less toxic in patients with non-squamous histology. Moreover, data from large phase III trials demonstrated that maintenance therapy with pemetrexed, docetaxel or erlotinib is an effective strategy against metastatic NSCLC. Overall, the changing paradigm in first-line treatment of NSCLC inevitably is changing the second-line strategy. In addition, the emerging role of maintenance therapy is leading to early use of all agents potentially active in a second- or third-line setting, with the consequence that very few options are available at disease progression. The aim of this article is to discuss the consequences of targeted treatments for second-line therapy in metastatic NSCLC.

Key words: epidermal growth factor receptor, erlotinib, gefitinib, NSCLC, pemetrexed

Introduction

In 2010, lung cancer unfortunately continues to lead cancer-related death worldwide [1]. Although a slight decline in the overall incidence of this disease has been recently registered in Western countries, its incidence in developing countries is still rising. Despite therapeutic advances, the prognosis of lung cancer remains poor, and the overall cure rate is <15%. Chemotherapy and radiation therapy used in the management of advanced non-small cell lung cancer (NSCLC) are associated with significant therapeutic and safety limitations. These limitations can cause poor outcome in terms of disease control and overall survival, thus emphasizing the need for treatment approaches that demonstrate efficacy in specifically targeting tumor cells. Given the rapid advances in the molecular and biological understanding of the disease process, carcinogenesis, angiogenesis and cell growth regulation, several new strategies have emerged for the treatment of NSCLC.

During the last 5 years, agents targeting the epidermal growth factor receptor (EGFR) or the vascular endothelial growth factor (VEGF) have significantly prolonged survival when used alone or in combination with chemotherapy [2–4]. Among targeted agents, the multitarget antifolate pemetrexed significantly prolonged survival over gemcitabine when given in combination with cisplatin as a first-line setting in patients with adenocarcinoma histology [5]. More recently, data from large phase III trials demonstrated that maintenance therapy with pemetrexed, docetaxel or erlotinib is an effective strategy against metastatic NSCLC [6–8]. Overall, the changing paradigm in the first-line treatment of NSCLC inevitably is changing the second-line strategy. The aim of the present article is to discuss the consequences of targeted treatments for second-line therapy in metastatic NSCLC.

The New Paradigm for First-Line Treatment of Metastatic NSCLC

For decades, NSCLC has been treated with chemotherapy irrespective of histology. Moreover, knowledge of tumor biology was limited, precluding any selection based on molecular markers.

As illustrated in Table 1, several targeted agents are currently available against NSCLC in the first-line setting, including the EGFR-tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib, the monoclonal antibodies cetuximab and bevacizumab, and the multitarget antifolate pemetrexed.

Data from large phase III trials leading, with the exception of cetuximab, to the approval of the above-mentioned drugs, demonstrated that, in 2010, we cannot select a therapy without an accurate definition of tumor histology and EGFR status. Patients harboring an EGFR-activating mutation have a better prognosis and certainly are extremely sensitive to EGFR-TKIs, while other agents, such as bevacizumab or pemetrexed, are less toxic and more effective in patients with non-squamous histology.
EGFR-TKIs in NSCLC

Gefitinib and erlotinib are selective EGFR-TKIs with demonstrated activity in pre-treated NSCLC. Large phase II and III trials evaluated the activity of EGFR-TKIs as a single agent or in combination with chemotherapy versus chemotherapy alone, as listed in Tables 2 and 3. These trials led to three relevant conclusions: (i) the addition of EGFR-TKI to standard chemotherapy is not more effective than chemotherapy alone [9–13]; (ii) EGFR-TKIs are equally effective as single-agent chemotherapy in both the first- and second-line setting [14–18]; and (iii) gefitinib and erlotinib treatments are inferior to standard first-line platinum-based chemotherapy in unselected NSCLC [19].

Recent data demonstrated that testing patients for EGFR mutation is critical for proper selection when choosing a first-line therapy. Four large phase III trials compared the EGFR-TKI gefitinib versus standard platinum-based chemotherapy in first-line metastatic NSCLC [20–23]. The first two trials, the IPASS [20] and First-SIGNAL [21], were conducted in chemonaive NSCLC patients who were selected based on clinical characteristics. Both trials included only Asian patients with adenocarcinoma histology, and the vast majority of included patients were female and never smokers. In the IPASS study [20], including 1217 patients, the primary end point of progression-free survival (PFS) was met, showing a significant reduction in the risk of progression for patients treated with gefitinib [hazard ratio (HR) 0.74, P < 0.0001]. In the First-SIGNAL trial [21], including 309 Korean patients, gefitinib significantly improved PFS (HR 0.81, P = 0.044) and offered better quality of life when compared with chemotherapy. Importantly, neither trial demonstrated any difference in survival, possibly due to the post-study use of EGFR-TKIs in the vast majority of patients of the chemotherapy arm. The most relevant aspect of both IPASS and First-SIGNAL trials was that the PFS improvement favoring gefitinib was confined to patients harboring an activating EGFR mutation. The group of patients with an EGFR wild-type tumor had a significantly longer PFS when treated with chemotherapy, while the opposite was observed among patients with EGFR mutations. These findings provide strong evidence that clinical predictors cannot be used in clinical practice for selection of NSCLC candidates for first-line therapy, and that, even in a patient population with all predictors for EGFR-TKI sensitivity (Asiatic, never smoker, female, adenocarcinoma), in the absence of an EGFR mutation, chemotherapy remains the gold standard. Conversely, in the presence of an EGFR mutation, although even in this specific subgroup no difference in survival was detected, gefitinib should be preferred to chemotherapy because of the higher response rate (RR), longer PFS and better quality of life.

More recently, two additional trials compared standard platinum-based chemotherapy with gefitinib in patients who were selected on the basis of biological characteristics. The WJTOG 3405 [22] and NEJ002 trials [23] randomly assigned chemonaive NSCLC patients harboring an EGFR mutation to gefitinib or platinum-based chemotherapy (carboplatin plus paclitaxel in NEJ002 and cisplatin plus docetaxel in WJTOG 3405). Both trials demonstrated that in NSCLC patients with EGFR mutations gefitinib produces a higher RR and longer PFS than standard chemotherapy, further supporting the use of an EGFR-TKI in the first-line setting in selected patients. A similar approach is currently being explored in Europe by investigators of the EURTAC trial, a randomized phase III study of erlotinib versus chemotherapy in chemonaive patients with EGFR-mutant NSCLC (EudraCT 2006-003568-73, NCT00446225).

### Table 1. Targeted agents available for first-line NSCLC therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regulatory approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FDA</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>In combination with carboplatin and paclitaxel for non-squamous NSCLC (at a dose of 15 mg/kg)</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>In combination with cisplatin for non-squamous NSCLC</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Application submitted for the first-line treatment of patients with advanced NSCLC in combination with platinum-based chemotherapy (cisplatin/vinorelbine) but application withdrawn because of issues related to the drug formulation</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Application for use as a first-line maintenance treatment with overall survival data of the SATURN trial added to the application</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>EMEA</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>In combination with platinum-based chemotherapy, for other than predominantly squamous NSCLC (at a dose of 7.5 or 15 mg/kg)</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>In combination with cisplatin for patients with other than predominantly squamous NSCLC</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>As monotherapy for maintenance treatment of patients with other than predominantly squamous NSCLC not progressed immediately following platinum-based chemotherapy</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Negative opinion, recommending the refusal of an extension of indication to add the treatment of NSCLC to the marketing authorization</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>As a single agent for NSCLC patients with activating mutations of EGFR-TKI, in all lines of therapy</td>
</tr>
</tbody>
</table>

EMEA, European Medicines Agency; FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer.
anti-EGFR monoclonal antibodies

The anti-EGFR antibody most widely tested in NSCLC is cetuximab, a chimeric human–murine IgG monoclonal antibody that binds to the extracellular domain of EGFR. In pre-clinical studies, cetuximab inhibited the growth of lung cancer cell lines and mouse xenografts, particularly in combination with chemotherapy [24].

In NSCLC, a phase II study of cetuximab monotherapy in pre-treated patients with advanced disease showed a response rate of 4.5% with an overall survival (OS) comparable with that achieved with other drugs approved for second-line treatment, such as pemetrexed, docetaxel or erlotinib [25]. Early phase I–II trials of cetuximab plus chemotherapy showed encouraging responses and median survival, thus supporting further investigations of combination regimens [25–27].

In order to investigate the best way to combine cetuximab with chemotherapy, the Southwest Oncology Group (SWOG) conducted a randomized phase II trial (S0342) comparing chemotherapy (carboplatin–paclitaxel) and cetuximab in concurrent versus sequential treatment (the same chemotherapy followed by cetuximab) in untreated advanced NSCLC [28]. In this study, in which 106 patients were assigned to the concurrent treatment and 117 to the sequential approach, no difference in RR and PFS was observed. Nevertheless, median survival was 11 months in both arms, thus suggesting that the addition of cetuximab to chemotherapy had the potential to improve survival as compared with chemotherapy alone.

The results of two large phase III trials, FLEX and BMS099, comparing standard chemotherapy versus chemotherapy plus cetuximab have been recently published [29, 30]. The FLEX trial [29] was a large phase III study randomly assigning EGFR-expressing patients to cisplatin–vinorelbine or the same regimen plus cetuximab. A total of 1688 patients were screened, of which 1442 (85%) were EGFR positive by immunohistochemistry, and 1125 were enrolled into the trial. The results of two large phase III trials, FLEX and BMS099, comparing standard chemotherapy versus chemotherapy plus cetuximab have been recently published [29, 30]. The FLEX trial [29] was a large phase III study randomly assigning EGFR-expressing patients to cisplatin–vinorelbine or the same regimen plus cetuximab. A total of 1688 patients were screened, of which 1442 (85%) were EGFR positive by immunohistochemistry, and 1125 were enrolled into the trial. In this study, the addition of cetuximab to chemotherapy led to a significant improvement in RR (36% versus 29%, \( P = 0.007 \)) and median survival (17.1 versus 17.4, \( P = 0.012 \)) in EGFR-positive patients, with an associated increased risk of side effects, particularly febrile neutropenia.

These results have been confirmed in the BMS099 study [30], which randomly assigned 676 chemo-naive NSCLC patients to carboplatin plus a taxane versus the same chemotherapy regimen plus cetuximab. Importantly, patients were enrolled in the BMS099 study regardless of EGFR expression. Although the primary end point of PFS was not met (4.4 versus 4.2 months, \( P = 0.2 \)), both the RR (25% versus 17%, \( P = 0.007 \)) and median survival (9.6 versus 8.3 months) favored the cetuximab arm, and the reduction in the risk of death was comparable with the FLEX trial (HR 0.89) although not statistically significant (\( P = 0.17 \)). The survival results observed in the FLEX and BMS099 trials clearly indicated that there is a consistent portion of NSCLC patients deriving no or little benefit from cetuximab therapy, thus highlighting the importance of proper patient selection.

Table 2. Randomized trials with EGFR-TKI single agent versus chemotherapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>Phase</th>
<th>Line</th>
<th>Drug</th>
<th>RR %</th>
<th>( P )</th>
<th>PFS Median (months)</th>
<th>( P )</th>
<th>HR</th>
<th>OS Median (months)</th>
<th>( P )</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>INVITE [14]</td>
<td>196</td>
<td>II</td>
<td>I</td>
<td>Gefitinib versus vinorelbine</td>
<td>3.1 versus 5.1</td>
<td>NR</td>
<td>2.7 versus 2.9</td>
<td>0.3</td>
<td>1.19</td>
<td>5.9 versus 8.0</td>
<td>NR</td>
<td>0.98</td>
</tr>
<tr>
<td>Lilenbaum [19]</td>
<td>103</td>
<td>II</td>
<td>I</td>
<td>Erlotinib versus CB</td>
<td>4.0 versus 12.0</td>
<td>0.13</td>
<td>1.9 versus 3.5</td>
<td>0.06</td>
<td>1.45</td>
<td>6.4 versus 9.7</td>
<td>0.018</td>
<td>1.73</td>
</tr>
<tr>
<td>IPASS [20]</td>
<td>1217</td>
<td>III</td>
<td>I</td>
<td>Gefitinib versus CB</td>
<td>34.0 versus 32.3</td>
<td>&lt;0.001</td>
<td>5.7 versus 5.8</td>
<td>&lt;0.001</td>
<td>0.74</td>
<td>18.6 versus 17.3</td>
<td>NS</td>
<td>0.91</td>
</tr>
<tr>
<td>Kobayashi [23]</td>
<td>198</td>
<td>III</td>
<td>I</td>
<td>Gefitinib versus CB</td>
<td>47.5 versus 29.0</td>
<td>&lt;0.001</td>
<td>10.4 versus 5.5</td>
<td>&lt;0.001</td>
<td>0.35</td>
<td>28.0 versus 23.6</td>
<td>NS</td>
<td>0.35</td>
</tr>
<tr>
<td>Lee [21]</td>
<td>313</td>
<td>III</td>
<td>I</td>
<td>Gefitinib versus GC</td>
<td>53.3 versus 45.3</td>
<td>0.15</td>
<td>6.1 versus 6.6</td>
<td>0.04</td>
<td>0.81</td>
<td>21.3 versus 23.3</td>
<td>NR</td>
<td>1.0</td>
</tr>
<tr>
<td>WITTOG [22]</td>
<td>177</td>
<td>III</td>
<td>I</td>
<td>Gefitinib versus DC</td>
<td>56.3 versus 25.3</td>
<td>0.15</td>
<td>9.2 versus 6.3</td>
<td>&lt;0.001</td>
<td>0.48</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>INTEREST [18]</td>
<td>1466</td>
<td>III</td>
<td>I</td>
<td>Gefitinib versus docetaxel</td>
<td>9.1 versus 7.6</td>
<td>0.3</td>
<td>2.2 versus 2.7</td>
<td>0.47</td>
<td>1.04</td>
<td>7.6 versus 8.0</td>
<td>1.02</td>
<td></td>
</tr>
<tr>
<td>V15-32 [15]</td>
<td>489</td>
<td>III</td>
<td>I</td>
<td>Gefitinib versus docetaxel</td>
<td>22.5 versus 12.8</td>
<td>0.009</td>
<td>2.0 versus 2.0</td>
<td>0.33</td>
<td>0.90</td>
<td>11.5 versus 14.0</td>
<td>0.33</td>
<td>1.12</td>
</tr>
<tr>
<td>SIGN [16]</td>
<td>141</td>
<td>II</td>
<td>I</td>
<td>Gefitinib versus docetaxel</td>
<td>13.2 versus 13.7</td>
<td>NS</td>
<td>3.0 versus 3.4</td>
<td>NS</td>
<td>0.94</td>
<td>7.5 versus 7.1</td>
<td>NS</td>
<td>0.97</td>
</tr>
<tr>
<td>ISTANA [17]</td>
<td>161</td>
<td>III</td>
<td>I</td>
<td>Gefitinib versus docetaxel</td>
<td>28.1 versus 7.6</td>
<td>0.0007</td>
<td>3.3 versus 3.4</td>
<td>0.044</td>
<td>0.73</td>
<td>NR</td>
<td>0.61</td>
<td></td>
</tr>
</tbody>
</table>

CB, carboplatin–paclitaxel; DC, docetaxel–cisplatin; GC, gemcitabine–cisplatin; HR, hazard ratio; NR, not reported; NS, not significant; OS, overall survival; PFS, progression-free survival; RR, response rate.

Table 3. Randomized trials of EGFR-TKI plus chemotherapy versus chemotherapy alone

<table>
<thead>
<tr>
<th>Reference</th>
<th>No.</th>
<th>Phase</th>
<th>Line</th>
<th>Drug</th>
<th>RR %</th>
<th>( P )</th>
<th>PFS Median (months)</th>
<th>( P )</th>
<th>HR</th>
<th>OS Median (months)</th>
<th>( P )</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTACT 1 [9]</td>
<td>1093</td>
<td>III</td>
<td>I</td>
<td>Gefitinib + GC versus GC</td>
<td>50.3 versus 47.2</td>
<td>NS</td>
<td>5.8 versus 6.0</td>
<td>0.7</td>
<td>9.9 versus 10.9</td>
<td>0.4</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>INTACT 2 [10]</td>
<td>1037</td>
<td>III</td>
<td>I</td>
<td>Gefitinib + CP vsCP</td>
<td>30.428.7</td>
<td>NS</td>
<td>5.3 versus 5.0</td>
<td>0.056</td>
<td>9.8 versus 9.9</td>
<td>0.6</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>TRIBUTE [11]</td>
<td>1059</td>
<td>III</td>
<td>I</td>
<td>Erlotinib + CP versus CP</td>
<td>21.5 versus 19.3</td>
<td>0.3</td>
<td>5.1 versus 4.9</td>
<td>0.3</td>
<td>0.93</td>
<td>10.6 versus 10.5</td>
<td>0.9</td>
<td>0.99</td>
</tr>
<tr>
<td>TALENT [12]</td>
<td>1172</td>
<td>III</td>
<td>I</td>
<td>Erlotinib + GC versus GC</td>
<td>31.5 versus 29.9</td>
<td>NS</td>
<td>5.4 versus 5.6</td>
<td>0.7</td>
<td>0.98</td>
<td>9.9 versus 10.1</td>
<td>0.4</td>
<td>1.06</td>
</tr>
<tr>
<td>FASTACT [13]</td>
<td>150</td>
<td>II</td>
<td>I</td>
<td>Erlotinib + GP versus GP</td>
<td>35.5 versus 24.4</td>
<td>0.12</td>
<td>6.7 versus 5.4</td>
<td>0.0002</td>
<td>0.47</td>
<td>17.1 versus 17.4</td>
<td>0.42</td>
<td>1.09</td>
</tr>
</tbody>
</table>

CP, carboplatin–paclitaxel; EGFR-TKI, epidermal growth factor receptor-thymidine kinase inhibitor; GC, gemcitabine–cisplatin; HR, hazard ratio; GP, gemcitabine combined with cisplatin or carboplatin; NR, not significant; OS, overall survival; PFS, progression-free survival; RR, response rate.
selection. Unfortunately, in both the BMS099 and FLEX trials, no biomarker, including KRAS mutation, EGFR mutation or EGFR gene copy number, demonstrated any clinical relevance for patient selection [31, 32]. Although there is no reliable biomarker that we can use in clinical practice for selection of patients who are candidates for cetuximab therapy and although the European Medicines Agency (EMEA) released a negative opinion for the addition of cetuximab to standard chemotherapy in NSCLC, the modest but significant survival impact observed in the FLEX trial indicates the drug as a potential option for some patients in the first-line setting.

antiangiogenesis—bevacizumab

Bevacizumab is a humanized monoclonal antibody directed against VEGF. Evidence regarding its efficacy in combination with first-line platinum-based doublet chemotherapy comes from two large randomized, phase III trials. ECOG 4599, conducted in the USA [33] and AVAil, conducted mainly in Europe, Australia and Canada [34]. In both trials, the anti-VEGF antibody was administered concurrently with first-line chemotherapy in patients with non-squamous histology. Subsequently, for patients who completed the planned six cycles of chemotherapy without disease progression, bevacizumab was continued as single-agent treatment until progression or unacceptable toxicity.

The ECOG 4599 trial tested the addition of bevacizumab to carboplatin plus paclitaxel [33]. In the experimental arm, bevacizumab was administered at a dose of 15 mg/kg every 3 weeks. In the study population of 878 patients, the addition of bevacizumab to chemotherapy produced a statistically significant improvement in OS [median 12.3 months versus 10.3 months, HR 0.79, 95% confidence interval (CI) 0.67–0.92, \( P = 0.003 \)]. Patients receiving bevacizumab also showed a significant improvement in PFS (HR 0.66; \( P < 0.001 \)), and in objective RR (35 versus 15%, \( P < 0.001 \)).

The AVAil trial was designed to replicate the results obtained in ECOG 4599, testing the addition of bevacizumab to cisplatin plus gemcitabine, a chemotherapy regimen widely used outside the USA [34]. Eligible patients were randomized to receive (i) chemotherapy plus placebo (347 patients); (ii) chemotherapy plus bevacizumab 7.5 mg/kg (345 patients); and (iii) chemotherapy plus bevacizumab 15 mg/kg (351 patients). The study was initially designed with OS as the primary end point, but this was amended to PFS. The improvement in PFS for the two arms treated with bevacizumab compared with the placebo group was statistically significant, although small in absolute terms. Median PFS was 6.1, 6.7 and 6.5 months in the chemotherapy-alone, chemotherapy plus bevacizumab 7.5 mg/kg and chemotherapy plus bevacizumab 15 mg/kg arms, respectively. HRs of progression with control were 0.75 and 0.82 for the lower and higher doses of bevacizumab, respectively. Although the AVAil trial failed to demonstrate any survival difference between standard and experimental arms, both the US Food and Drug Administration (FDA) and EMEA approved bevacizumab for first-line treatment of advanced, non-squamous NSCLC, in combination with carboplatin plus paclitaxel or any platinum-based chemotherapy, respectively.

It is relevant to note that in both the ECOG and AVAil trials, bevacizumab was administered until disease progression. The optimal duration of bevacizumab therapy remains an open issue even if pre-clinical data suggest that the treatment should be continued at least until disease progression [35]. The identification of predictive factors of efficacy would be relevant for the optimal use of the drug, but to date there are no validated biomarkers that predict response to VEGF inhibitors. Recent data from studies in lung [36], colon and renal cancer suggested that treatment-related hypertension could be a surrogate marker of efficacy of bevacizumab. This observation needs a prospective validation.

pemetrexed

Pemetrexed is an antifolate that inhibits multiple enzymes involved in purine and pyrimidine synthesis. Thymidylate synthase (TS) is the primary target of pemetrexed, and dihydrofolate reductase and glycaminide ribonucleotide formyl transferase are secondary targets.

The first phase III study of pemetrexed in NSCLC established similar efficacy and a better safety profile for pemetrexed when compared with docetaxel in the second-line setting [37]. In a retrospective analysis of this trial, a significant association was identified between histology and efficacy outcome for pemetrexed [38].

A second phase III study demonstrated non-inferiority and better tolerability for cisplatin plus pemetrexed than for cisplatin plus gemcitabine in chemo naïve NSCLC [5]. Because of the emerging evidence of a differential expression of TS between adenocarcinoma and squamous cell carcinoma, a pre-specified subgroup analysis by histology was conducted. Importantly, the benefit in terms of survival was confined to patients with non-squamous histology assigned to the pemetrexed arm, with a potential detrimental effect for squamous patients. Based on these data, pemetrexed use was restricted to patients with non-squamous histology, highlighting, for the first time in NSCLC, the relevance of histology for patient selection.

the ‘maintenance’ strategy

The role of maintenance therapy after first-line chemotherapy remains controversial even if recent data supported its use. Data from large phase III trials [39, 40] showed that ~50% of metastatic NSCLC patients treated with first-line chemotherapy were not able to receive an effective second-line option. This was mainly because of deterioration of performance status due to the aggressiveness of the disease. Therefore, there is the clinical need to ensure that the vast majority of our patients are able to receive agents that have been demonstrated to prolong their survival significantly. Therefore, the expected survival benefit of maintenance therapy is not because a second-line agent is more effective when given early, but simply because this strategy ensures that the vast majority of patients receive an effective drug before the detrimental effect of disease progression. Different terms have been used to define this strategy, such as maintenance, early second-line or consolidation, with no consensus on the most appropriate terminology.
Two phase III trials investigated the role of maintenance chemotherapy in NSCLC [41, 42]. In both studies, patients receiving docetaxel or pemetrexed immediately after first-line chemotherapy survived longer than patients in the control arm, with a difference that was statistically significant only in the pemetrexed trial in patients with non-squamous histology [42]. Three trials investigated the role of targeted agents in the maintenance setting [8, 43, 44] and all demonstrated a significant prolongation in PFS, with a benefit in terms of survival statistically significant only in the trial with erlotinib [8]. Overall, data from maintenance studies indicate that maintenance therapy is at least an option that we should discuss with our patients, with a consequent effect on the algorithm for second-line therapy.

**effects of first-line and maintenance therapy on second-line treatment options**

At present, few drugs have received approval in the second-line setting: docetaxel, pemetrexed and the TKIs gefitinib and erlotinib. The new first-line strategy against NSCLC and the emerging role of maintenance therapy are leading to early use of all agents potentially active in the second- or third-line setting, with the consequence that very few options are available at disease progression. Identification of mechanisms involved in drug resistance could be useful in clinical practice for choosing the best treatment.

In patients with an EGFR mutation exposed to reversible EGFR-TKIs, such as erlotinib or gefitinib, two main mechanisms are involved in acquired resistance. The first mechanism has been represented by the acquisition of a secondary mutation in the EGFR tyrosine kinase domain, the T790M substitution [45]. This event occurs in ~50% of the patients with EGFR-sensitizing mutations that develop resistance to gefitinib or erlotinib. Another mechanism implicated in acquired resistance to EGFR-TKIs is MET amplification. In this model, that has been observed in ~20% of EGFR-mutant patients initially responding to gefitinib or erlotinib, resistant cells maintain activation of the phosphatidylinositol 3-kinase (PI3K) pathway via MET amplification [46]. In vitro observations suggest that resistant tumor cells present a double oncogene addiction and that they require combined EGFR and MET inhibition for efficient growth inhibition [47]. These findings have led to the clinical development of strategies to inhibit MET effectively in NSCLC and clearly indicate that in clinical practice it is not recommended to propose a second-line therapy with a reversible EGFR-TKI in a patient progressing while on treatment with gefitinib or erlotinib.

Another important aspect in clinical practice is whether the use of cetuximab in the first-line setting could impair the efficacy of erlotinib or gefitinib given as second-line treatment. At present we have very few data available. Mukohara et al. analyzed the effect of both cetuximab and gefitinib in NSCLC cell lines with or without EGFR mutation [48]. In this study, demonstrating that EGFR mutations are associated with sensitivity to gefitinib but not to cetuximab, the authors also analyzed the outcome of four NSCLC patients with EGFR mutation who were treated with gefitinib or cetuximab for relapsed disease. Three patients received cetuximab in first-line treatment. Achieving stable disease as their best response. At progression, these three patients switched to gefitinib and all achieved a partial response. Although these data are anecdotal and need to be confirmed in larger studies, at present there is no evidence that patients pre-treated with cetuximab should not be treated with an EGFR-TKI in second-line treatment.

In phase III trials, bevacizumab was used in combination with chemotherapy and after the completion of platinum-based therapy as maintenance until disease progression. Pre-clinical data demonstrated a very rapid tumor regrowth once the bevacizumab therapy was suspended, suggesting that the drug should be used at least until disease progression and probably continued even in the presence of progression. Clinical data support this concept. In colorectal cancer, the use of bevacizumab beyond first progression was associated with prolonged survival [49]. Nevertheless, the negative results observed with bevacizumab in the second-line setting [50], together with the absence of definitive data in NSCLC, do not support the routine use of the drug in second-line treatment irrespective of the therapy previously received.

Based on the above-discussed data, how should we choose the best second-line option in NSCLC? Figure 1 illustrates the paradigm for second-line therapy. In general, second-line therapy includes drugs not previously used even if, in patients progressing after at least 6 months since the completion of first-line therapy, the same treatment could be reconsidered. Factors influencing the decision most are clinical parameters, such as previous therapies and histology, patient preferences (oral versus intravenous) and biological characteristics, particularly EGFR status. Patients with EGFR mutations are extremely sensitive to erlotinib or gefitinib, and, even in situations in which a second-line option is not offered (i.e. low performance status), a treatment with such a drug cannot be denied and, therefore, if not previously used, an EGFR-TKI represents the first choice.

In EGFR wild-type patients, EGFR-TKIs remains the best option in EGFR-TKI-naive squamous cell carcinoma, considering the better toxicity profile and the non-inferiority in...
terms of survival demonstrated in a large phase III trial comparing gefitinib versus docetaxel [18]. Moreover, data from the BR21 trial, comparing erlotinib versus placebo in pre-treated NSCLC showed a significant survival benefit of erlotinib irrespective of histology, with a higher reduction in the risk of death in squamous cell carcinoma than in adenocarcinomas [3].

At present there is no published trial directly comparing pemetrexed with an EGFR-TKI in second-line treatment. The results of the TITAN study, a phase III trial comparing erlotinib versus docetaxel or pemetrexed in NSCLC patients progressing after four cycles of platinum-based chemotherapy, are not currently available. Indirect comparison suggests that erlotinib and pemetrexed have similar efficacy in pre-treated patients [18, 37] and therefore in EGFR-TKI- and pemetrexed-naïve individuals, patient preference should guide the clinical decision. In conclusion, although many drugs are currently available against NSCLC, the majority of them are used as first-line, and very few options are available at disease progression.

Improvement in knowledge of tumor biology is contributing to the identification of new drugs potentially active and useful for prolonging survival of relapsed patients.

disclosure

All authors declare no conflict of interest.

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