Review of the pemetrexed and gemcitabine combination in patients with advanced-stage non-small cell lung cancer

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Pemetrexed is a new multitargeted antifolate that can be easily administered as a 10-min infusion every 3 weeks. The use of folic acid, vitamin B12, and corticoid prophylaxis has significantly reduced pemetrexed-induced toxicity. Single-agent pemetrexed has shown antitumor activity in a wide range of solid tumors, including non-small cell lung cancer (NSCLC). Association with vinorelbine, cisplatin, carboplatin, and oxaliplatin have been tried, but the pemetrexed and gemcitabine combination, an easy to administer cisplatin-free doublet, has been documented in many phase 2 trials in the first-line treatment of advanced NSCLC. In vitro cytotoxic assays and phase I studies have defined several schedules of administration for pemetrexed and gemcitabine. The recommended dose is pemetrexed 500 mg/m² on day 1 or 8, and gemcitabine 1250 mg/m² on day 1 and 8, but it is unknown if pemetrexed should precede or follow gemcitabine and at what time interval. Published studies have failed to show significant differences in overall survival times despite response rates oscillating between 15% and 41%. The main toxicities are neutropenia, fatigue, skin rashes and elevated transaminases and seem to occur with similar rates in the many phase 2 trials. Hopes for the future are in tailored chemotherapy, since molecular markers of sensitivity are available for gemcitabine and pemetrexed, allowing to determinate in the future which patients will be most likely to benefit from the gemcitabine-pemetrexed doublet.

Key words: cisplatin-free doublet, gemcitabine, NSCLC, pemetrexed

introduction

Despite some advances in the treatment of advanced non-small cell lung cancer (NSCLC), the introduction of third-generation cytotoxic agents (vinorelbine, gemcitabine, docetaxel, irinotecan, and paclitaxel) has not achieved a breakthrough in the dismal prognosis of this disease. Several meta-analyses have proved the superiority of 2-drug chemotherapy and cisplatin-based chemotherapy, but no gold standard exists [1, 2]. Cisplatin-free doublets, which have less toxicity, have been investigated, and some combinations, such as vinorelbine-gemcitabine, are considered acceptable alternatives to the cisplatin-based regimen [3]. The purpose of this paper is to summarize the data of a new cytotoxic agent, pemetrexed, and its association with gemcitabine in the treatment of advanced NSCLC.

pemetrexed, a new antifolate with a wide range antitumor activity

Pemetrexed (Alimta®, Eli Lilly and Company, Indianapolis, USA) is a multitargeted antifolate that can be easily administered as a 10-minute infusion every 3 weeks. It is rapidly metabolized intracellularly to a pentaglutamate form, where it inhibits 3 enzymes (thymidylate synthase, dihydropfolate reductase, and glycinamide ribonucleotide transferase) involved in folate metabolism and DNA synthesis. Thus, the cytotoxicity of pemetrexed is caused by inhibition of both the pyrimidine and purine pathways [4]. In phase I studies, the maximum tolerated dose of pemetrexed was 600 mg/m² every 3 weeks. In several phase II trials, this dose was later reduced to 500 mg/m² every 2 weeks, particularly when combined with other cytotoxic agents [5]. When a safety analysis from multiple pemetrexed trials sought to decrease pemetrexed-induced toxicity, folic acid and vitamin B12 supplementation became a requirement for pemetrexed-based therapy [6]. In a phase III trial for patients with malignant pleural mesothelioma, pemetrexed-cisplatin with vitamin supplementation demonstrated less toxicity than the same arm without supplementation. The combination arm showed better efficacy than the cisplatin single agent arm [7]. As a single agent, pemetrexed has shown antitumor activity in a wide range of solid tumors, including breast, colon, pancreatic, and NSCLC [8].

As first-line chemotherapy in advanced NSCLC, single-agent pemetrexed, without vitamin supplementation, was
tested in 2 phase II trials by Clarke et al. [9] and Rusthoven et al. [10].

Clarke et al. reported a 16% response rate and a median survival of 7.2 months. Rusthoven et al. reported a 23.3% response rate and a median survival of 9.2 months. In these 2 studies, the main toxicities were grade 3/4 neutropenia (Clarke, 42%; Rusthoven, 39%) and grade 3/4 skin rash (31%, 39%). As second-line chemotherapy in NSCLC, a phase III trial recently demonstrated that single-agent pemetrexed, with vitamin supplementation, had less toxicity than docetaxel, and both arms had similar efficacy [11].

**gemcitabine, an antimetabolite used against a wide range of cancer**

Gemcitabine (GEMZAR®, Eli Lilly and Company, Indianapolis, IN) is a pyrimidine antimetabolite that is intracellularly transformed to difluorodeoxycytidine triphosphate. Its incorporation into DNA results in chain termination. Gemcitabine also inhibits ribonucleotide reductase, an enzyme required for deoxynucleoside formation and DNA synthesis [12]. Gemcitabine as a single agent or in combination, most of the time with a platinum compound, is now a widely used chemotherapy for the treatment of many cancers such as lung cancer (including small cell lung cancer), pancreatic cancer, breast cancer, lymphoma, ovarian cancer and bladder cancer.

As first-line chemotherapy in advanced NSCLC, single-agent gemcitabine has shown activity in several phase II trials. Anderson et al. [13] used single-agent gemcitabine 800 mg/m² weekly for 3 weeks followed by 1 week of rest. During the trial, the gemcitabine dose was increased to 1000 mg/m². Overall, the response rate was 20% with a median survival of 7 months. The primary grade 3/4 toxicities were hematologic in nature. In another trial, Abratt et al. [14] used gemcitabine 1000 mg/m² weekly for 3 weeks followed by 1 week of rest. During the trial, the gemcitabine dose was increased to 1250 mg/m². The response rate was 20% with a median survival of 9.2 months. Overall, hematologic toxicity was negligible. Another trial by Gatzemeier et al. [15] used gemcitabine 1250 mg/m² weekly for 3 weeks followed by 1 week of rest. For 161 patients, the response rate was 21.8% with a median survival of 9.4 months. The primary grade 3/4 toxicities were neutropenia, elevated transaminases, and nausea/vomiting.

In the phase III setting, gemcitabine-cisplatin has been tested in 28-day and 21-day cycles as first-line treatment of NSCLC. Using 28-day cycles, Sandler et al. compared gemcitabine-cisplatin (1000/100 mg/m²) to single-agent cisplatin (100 mg/m²) [16]. The gemcitabine-cisplatin arm reported a significantly higher response rate and a significantly longer median survival than the cisplatin arm. Using 21-day cycles, Cardenal et al. compared gemcitabine-cisplatin (1250/100) to etoposide-cisplatin (100/100 mg/m²) [17]. The gemcitabine-cisplatin arm reported a significantly higher response rate, and the 2 arms had similar median survival. Both of these gemcitabine-cisplatin regimens were approved by the FDA for first-line treatment in NSCLC.

**pemetrexed–gemcitabine, a synergistic combination**

Because pemetrexed and gemcitabine have shown single-agent activity against a wide range of solid tumors, the combination of these two agents was evaluated *in vitro*, and cytotoxic synergy was found when gemcitabine preceded pemetrexed [18]. A better molecular comprehension has reinforced the synergistic cytotoxicity concept of these 2 agents, showing *in vitro* that pemetrexed significantly decreased the amount of phosphorylated Akt and enhanced apoptosis [19]. However, another *in vitro* study found that the inverse sequence (pemetrexed followed by gemcitabine) was most effective [20].

The first phase I study tested gemcitabine followed by pemetrexed on day 1 with a 90-minute interval between administrations. During the study, the day-8 administration of pemetrexed was introduced to improve hematologic tolerance [21]. The study’s recommended phase II dose was gemcitabine 1250 mg/m² on days 1 and 8 followed by pemetrexed 500 mg/m² on day 8 of a 3-week cycle. The most common dose-limiting toxicity was neutropenia, and other toxicities included nausea, fatigue, rash, and elevated transaminases.

Another phase I study evaluated gemcitabine and pemetrexed in a 2-week schedule [22]. The recommended dose was gemcitabine 1500 mg/m² followed by pemetrexed 500 mg/m² on day 1 of a 2-week cycle. Further evaluation of this schedule has not yet been published.

Dy et al. [23] examined gemcitabine-pemetrexed in rapid sequence. Gemcitabine 1250 mg/m² was administered on days 1 and 8 of each 21-day cycle, and pemetrexed 500 mg/m² on day 8 immediately following gemcitabine administration. No increased toxicity was observed with this schedule in comparison to the previous phase I schedule and there was no pharmacokinetic interaction between the two drugs.

**pemetrexed–gemcitabine in advanced NSCLC**

The pemetrexed-gemcitabine combination has been evaluated as first-line chemotherapy of advanced NSCLC in several phase II trials (see Table 1) and in one neoadjuvant study.

In the first phase II study, Monnerat et al. [24] administered gemcitabine 1250 mg/m² on days 1 and 8 followed by pemetrexed 500 mg/m² on day 8 with a 90-min interval between infusions. After 13 patients were enrolled, folic acid and vitamin B₁₂ supplementation was added to lower pemetrexed-induced toxicity. Overall, 60 patients were enrolled, and 58 were evaluable for response. Nine patients had partial response for an overall response rate of 15.5%. Median survival was 10.1 months with a 1-year survival rate of 42%. Grade 3/4 toxicities were neutropenia (62%), febrile neutropenia (17%), fatigue (23%), and elevated aspartate aminotransferase (15%) and alanine aminotransferase (20%).

A second phase II study by Treat et al. [25] enrolled 46 patients, using a different schedule: gemcitabine 1250 mg/m² on days 1 and 8 and pemetrexed 500 mg/m² on day 1, immediately following gemcitabine, every 21 days. All patients received folic acid, vitamin B₁₂, and steroid
prophylaxis. Among 28 patients, the preliminary response rate was 32% [26].

Adjei et al. [27] conducted a randomized phase II trial, which tested 3 sequences of pemetrexed-gemcitabine. Contrary to the phase I study and the first in vitro studies, when pemetrexed preceded gemcitabine, better response rates were achieved with identical overall survival figures (Table 1). In all 3 sequences, the toxicity profile was similar.

McCleod et al. [28] conducted a study to prove that the therapeutic index was not compromised by eliminating the 90 minutes interval. Gemcitabine 1250 mg/m² was thus administrated on days 1 and 8 followed by pemetrexed 500 mg/m² on day 1 without interval between infusions.

Response rate was 31% and toxicity was comparable to the ones reported by Adjei et al. [27].

West et al. [29] performed a similar study by eliminating the 90-min interval but pemetrexed was given on day 8 and immediately before gemcitabine. Response rate was 41% and toxicity was comparable to the other studies.

In summary, pemetrexed-gemcitabine appears promising, but the optimal administration in terms of sequence and timing remains elusive. When evaluating the experience with this regimen, median survival times are generally similar across these phase II trials despite various response rates (Table 1). Schedule without time interval could be preferred because of their convenience of administration.

### Table 1. Pemetrexed in combination in the first-line treatment of advanced NSCLC

<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Chemotherapy, dose, schedule</th>
<th>N (E)</th>
<th>Stage III, IV</th>
<th>ORR</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monnerat [24]</td>
<td>Pemetrexed* 500 mg/m² d8 q3w</td>
<td>60 (58)</td>
<td>13%, 87%</td>
<td>15.5%</td>
<td>11.3 mo.</td>
</tr>
<tr>
<td>Treat [25; 26]</td>
<td>Gemcitabine 1250 mg/m² d1 q3w</td>
<td>48 (28)</td>
<td>11%, 89%</td>
<td>32.1%</td>
<td>NA</td>
</tr>
<tr>
<td>Adjei [27] [arm 1]</td>
<td>Pemetrexed/C160 500 mg/m² d1 q3w</td>
<td>58 (58)</td>
<td>14%, 86%</td>
<td>31%</td>
<td>11.4 mo.</td>
</tr>
<tr>
<td>Adjei [27] [arm 2]</td>
<td>Gemcitabine 1250 mg/m² d1 q3w</td>
<td>30 (30)</td>
<td>7%, 93%</td>
<td>8.7%</td>
<td>10.4 mo.</td>
</tr>
<tr>
<td>Adjei [27] [arm 3]</td>
<td>Pemetrexed/C224 500 mg/m² d1 q3w</td>
<td>60 (58)</td>
<td>13%, 87%</td>
<td>16.7%</td>
<td>11.6 mo.</td>
</tr>
<tr>
<td>McCleod [28]</td>
<td>Pemetrexed/C224 500 mg/m² d1 q3w</td>
<td>56 (56)</td>
<td>10%, 90%</td>
<td>30.8%</td>
<td>N.A.</td>
</tr>
<tr>
<td>West [29]</td>
<td>Pemetrexed/C224 500 mg/m² d1 q3w</td>
<td>47 (34)</td>
<td>10%, 90%</td>
<td>44.1%</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

NA, not available; N, number of patients; E, number of patients evaluable for tumor response; ORR, overall response rate; MS, median survival.

*Pemetrexed infused 90 minutes after gemcitabine.
/C160 Pemetrexed infused immediately after gemcitabine.
/C224 Pemetrexed infused 90 minutes before gemcitabine.
/C224 Pemetrexed infused immediately before gemcitabine.

### Table 2. Pemetrexed in combination with other chemotherapy in the first-line treatment of advanced NSCLC

<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Chemotherapy, dose, schedule</th>
<th>N (E)</th>
<th>Stage III, IV</th>
<th>ORR</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarke [31]</td>
<td>Pemetrexed 500 mg/m² d1 q3w</td>
<td>37 (35)</td>
<td>5%, 95%</td>
<td>40%</td>
<td>7.9 mo.</td>
</tr>
<tr>
<td>Manegold [32]</td>
<td>Vinorelbine 30 mg/m² d1 q3w</td>
<td>36 (36)</td>
<td>50%, 50%</td>
<td>39%</td>
<td>10.9 mo.</td>
</tr>
<tr>
<td>Shepherd [33]</td>
<td>Pemetrexed 500 mg/m² d1 q3w</td>
<td>31 (29)</td>
<td>16%, 84%</td>
<td>45%</td>
<td>8.9 mo.</td>
</tr>
<tr>
<td>Scagliotti [34] [arm 1]</td>
<td>Pemetrexed 500 mg/m² d1 q3w</td>
<td>39 (39)</td>
<td>38%, 62%</td>
<td>31.6%</td>
<td>10.5 mo.</td>
</tr>
<tr>
<td>Scagliotti [34] [arm 2]</td>
<td>Carboplatin AUC 6 d1 q3w</td>
<td>41 (41)</td>
<td>34%, 66%</td>
<td>26.8%</td>
<td>10.5 mo.</td>
</tr>
<tr>
<td>Zinner [35] [Europe]</td>
<td>Pemetrexed 500 mg/m² d1 q3w</td>
<td>39 (39)</td>
<td>34%, 66%</td>
<td>32%</td>
<td>10.5 mo.</td>
</tr>
<tr>
<td>Zinner [35] [MDACC]</td>
<td>Carboplatin AUC 6 d1 q3w</td>
<td>50 (50)</td>
<td>8%, 92%</td>
<td>29%</td>
<td>13.5 mo.</td>
</tr>
</tbody>
</table>

N, number of patients; E, number of patients evaluable for tumor response; ORR, overall response rate; MDACC, MD Anderson Cancer Center; MS, median survival.
In the neoadjuvant setting, 23 patients were evaluated by Bepler et al. [30] and were administered gemcitabine 1500 mg/m² and pemetrexed 500 mg/m² on days 1, 15, 29, and 43. None of the patients had disease progression, and the response rate among 15 evaluable patients was 33%. There were no deaths or unexpected morbidities related to surgery or chemotherapy. In terms of clinical response, the pemetrexed-gemcitabine is worthwhile to deserve further investigations as a neoadjuvant cisplatin-free doublet.

other pemetrexed combinations in the treatment of advanced NSCLC

Several other pemetrexed-containing regimens have been studied among chemonaive patients with NSCLC (Table 2).

In a phase I/II setting, Clarke et al. [31] tested pemetrexed-vinorelbine and obtained a promising 40% response rate, but the median survival was 7.9 months, which is relatively short. Febrile neutropenia occurred in 11% of the patients, and 1 infectious toxic death occurred.

Pemetrexed-cisplatin was tested in two phase II trials by Manegold et al. [32] and Shepherd et al. [33], Manegold et al. reported a 39% response rate with a median survival of 10.9 months and Shepherd et al. reported a 45% response rate with a median survival of 8.9 months. Grade 3 and 4 neutropenia was the predominant hematologic toxicity.

In a randomized phase II trial, Scagliotti et al. [34] compared pemetrexed with either carboplatin or oxaliplatin. In the pemetrexed-carboplatin arm, the response rate was 32%, and the median survival was 9.9 months. In the pemetrexed-oxaliplatin arm, the response rate was 27%, and the median survival was 8.3 months. For both arms, neutropenia was the predominant grade 3 and 4 toxicity (25.6% of pemetrexed-carboplatin patients, 7.5% of pemetrexed-oxaliplatin patients). Only 1 patient (2%) in the pemetrexed-carboplatin arm and 2 patients (5%) in the pemetrexed-oxaliplatin arm reported febrile neutropenia.

Zinner et al. [35] reported the results of two phase 2 studies performed in the MD Anderson Cancer Center and the other in Europe. Eighty-nine patients received carboplatin AUC6 and pemetrexed 500 mg/m² on day 1 of a 21 day-cycle. Results are quite comparable to the carboplatin arm of the Scagliotti’s study, showing a 29 to 32% response rate, a 10.5 to 13.5 months overall survival and a low rate of febrile neutropenia (2 to 5%).

future direction

The best pemetrexed-containing combination has yet to be established in a phase III trial [5]. A large, comparative phase III trial of pemetrexed-cisplatin versus gemcitabine-cisplatin in NSCLC is ongoing, which will determine the best antimitabolite drug to use with cisplatin.

The pemetrexed-gemcitabine combination is an attractive cisplatin-free doublet with low toxicity, but its ideal schedule of administration and direct comparison with other pemetrexed-based combinations are still lacking. However, the blind application of the many chemotherapy doublets remains unsatisfactory, despite the slight increase observed in the overall survival rate over the last 20 years. Tailored chemotherapy is the goal and biologic features of the tumoral tissue deserve closer examination. The clinical application of mRNA expression levels of amplified genes may disclose many genetic influences on cytotoxic drug sensitivity. This approach seems to be promising for the pemetrexed-gemcitabine combination since the assessment of ribonucleotide reductase subunit M1 and thymidylate synthase mRNA expression levels might select patients who could benefit most from gemcitabine or pemetrexed combinations [36]. Results of prospective trials are awaited to validate this promising approach of customized chemotherapy.

disclosures

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35. Zinner RG, Kortsik C, Dark GG et al. Pemetrexed plus carboplatin as first-line treatment for patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC): phase II results of a multicenter European trial and an MD Anderson Cancer Center (MDACC) trial. Lung Cancer 2005; 49 (suppl 2), S91 (abstract PO-039).