Gemcitabine: Single-Agent and Combination Therapy in Non-Small Cell Lung Cancer

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ABSTRACT

With the advent of several newer agents with single-agent response rates greater than 20% and approximately 30%-40% in combination therapy, non-small cell lung cancer (NSCLC) may now be considered a malignancy that is moderately sensitive to chemotherapy. Examples of these agents include the taxanes, paclitaxel and docetaxel; vinorelbine, a new vinca alkaloid, and the camptothecins, of which CPT-11 is the most actively studied agent. Another new and exciting agent is gemcitabine, a nucleoside analogue structurally related to cytosine arabinoside. Gemcitabine’s mechanism of action is activated by deoxycytidine kinase to dFdCMP, dFdCDP and dFdCTP. The latter two compounds, when incorporated into DNA, result in chain termination. Phase I studies using a short infusion schedule given weekly for three weeks followed by one week off established 1,000-1,250 mg/m²/week as the maximum tolerated dose. Single-agent gemcitabine has been extensively studied in patients with chemotherapy-naive advanced NSCLC with response rates of approximately 20%. Response rates for the combination of gemcitabine plus cisplatin are approximately 28%-54% in phase II trials. Recently, this combination has been studied in randomized phase II and III trials revealing improvements in response rates, time to progression and, in the phase III trial, survival. Current and future studies are evaluating gemcitabine in non-cisplatin combinations (i.e., taxanes). The Oncologist 1999;4:241-251

Non-small cell lung cancer (NSCLC) historically has been considered a malignancy that is refractory to most currently available chemotherapeutic agents. Of the more commonly used oncolytics, the most active agents are cisplatin, mitomycin-C, vinblastine, and etoposide with response rates in the 15%-25% range [1].

With the advent of several newer agents with single-agent response rates of approximately 20% and approximately 30%-40% in combination therapy, NSCLC may now be considered a malignancy that is moderately sensitive to chemotherapy. Examples of these agents include the taxanes, paclitaxel and docetaxel; vinorelbine, a new vinca alkaloid; and the camptothecins, of which CPT-11 is the most actively studied agent [2]. Another new and exciting agent is gemcitabine, a nucleoside analogue that is structurally related to cytosine arabinoside.

PRE-CLINICAL

Gemcitabine (difluorodeoxycytidine), an analogue of deoxycytidine, is a pyrimidine antimetabolite [3]. The mechanism of action of gemcitabine has been well characterized. Gemcitabine is deaminated and inactivated by deoxycytidine deaminase to difluorodeoxyuridine; or else it is activated by deoxycytidine kinase to dFdCMP, dFdCDP and dFdCTP. The latter is incorporated into DNA, resulting in chain termination. In comparison to cytosine arabinoside (ara-C) incorporation into DNA, dFdCTP is less readily excised from DNA by DNA exonuclease. This contributes to the accumulation of dFdCTP intracellularly to a greater degree than ara-C, which may account, in part, for its different spectrum of preclinical and clinical activity. In addition, gemcitabine inhibits ribonucleotide reductase, an enzyme that produces deoxynucleotides that are required for DNA synthesis [4]. Gemcitabine is active in a variety of murine solid tumors and leukemias, as well as several human tumor xenografts [4].

Phase I Studies

Initial phase I studies using a short infusion schedule given weekly for three weeks followed by one week off...
established 790 mg/m²/week as the maximum tolerated dose. Dose-limiting toxicity was myelosuppression with thrombocytopenia more significant than granulocytopenia [5]. Phase I-II trials have established 1,250 mg/m²/week as an optimal tolerated dose [6-8]. Principal toxicities reported were hematologic with grade 4 neutropenia/thrombocytopenia occurring rarely, reversible elevation in hepatic transaminases, proteinuria, mild skin rash ± pruritus, and nausea/vomiting. A review of 201 patients treated with 1,250 mg/m²/week who had not received prior chemotherapy confirmed these results. The incidence of neutropenia grade 3 and 4 was seen in 23% and 6%, respectively; reversible elevation in hepatic transaminases grade 3 and 4 was 6% and 2%, respectively; grade 3 proteinuria occurred in less than 1%; grade 3 nausea/vomiting was seen in 10%, and mild skin rash in 26% with pruritis occurring in 10% [9].

Other phase I studies have been conducted utilizing other more frequent dosing regimens (i.e., twice weekly and daily times five). These studies reported significantly more nonhematologic toxicities such as flu-like symptoms and rash with dose-limiting toxicity being thrombocytopenia [10, 11]. The daily times five phase I trial was stopped because of sporadic fever and occasional WHO grade 3/4 hypotension [11].

**Single-Agent Phase II Studies**

Gemcitabine has been studied extensively as a single agent in patients with previously untreated NSCLC (Table 1). The studies involved nearly 500 evaluable patients. Shepherd et al. reported on the results of four phase II gemcitabine trials in Europe and the United States [12-15]. The studies involved 332 evaluable patients with advanced inoperable NSCLC (54% stage IV). Gemcitabine was given by a short i.v. infusion weekly times three and repeated every four weeks. Starting gemcitabine doses were 800 mg/m² to 1,250 mg/m². Responses were seen in 20% of patients. Toxicity was again mild, with WHO grade 3/4 neutropenia occurring in 25% of patients (without significant clinical infections noted). WHO grade 3/4 thrombocytopenia was seen in only 2% of patients. Transient elevations of hepatic transaminases (WHO grade 3/4) were seen in 12% of patients. Other toxicities seen were transient rashes and lethargy (20% to 24% of patients). Fukuoka et al. from Japan reported on two phase II studies involving patients with NSCLC [16, 17]. Seventy-four patients with NSCLC (41 stage IV patients) were evaluable. Gemcitabine was given as a short i.v. infusion weekly times three with cycles repeated every four weeks. The starting dose of gemcitabine was 1,000 mg/m² to 1,250 mg/m². Responses were seen in 20 patients for an overall response rate of 27%. WHO grade 3/4 leukopenia was seen in <10% of patients.

**Cisplatin Combination Phase II Studies**

After establishing single-agent activity the next logical step was to combine gemcitabine with other active agents. Cisplatin is one of the most extensively studied agents in the treatment of metastatic NSCLC. Pooled data from ten phase II trials revealed an overall response rate of 21% [1]. Investigators have previously documented synergy between ara-C and cisplatin in LoVo colon carcinoma cells [18]. Gemcitabine, by being structurally related to ara-C, was felt to be potentially synergistic with cisplatin. Two recent abstracts from The Netherlands support this finding [19, 20].

Toward this end there have been seven studies involving the combination of cisplatin and gemcitabine [21-27]. All seven trials dosed gemcitabine weekly times three with one week off schedule. Five studies dosed cisplatin as a single dose either day 1, 2 or 15 [22-26]. Cycles were repeated every four weeks. Two studies dosed cisplatin on a weekly times three with one week off schedule, as well [26, 27]. The results of these trials are described in Table 2. In all studies toxicity was principally thrombocytopenia and neutropenia, but was mild with no reported episodes of clinical bleeding or neutropenic fevers.

Response rates in the monthly cisplatin trials ranged from 28% to 54%, with median survivals reported as 8.4 to 15.4 months. Given the small numbers of patients in these phase II trials and the variations in patient populations (i.e., the number of patients with stage III versus stage IV disease, performance status, etc.), it is difficult to compare response rates and survival. It is interesting to note, however, the difference in toxicities, particularly thrombocytopenia (Table 2). The studies administering cisplatin on day 1 or 2 were found to have an increased incidence of grade 3 and 4 thrombocytopenia (~50%) compared with the studies dosing cisplatin on day 15 (~25%). This outcome may be related to synergy between the cisplatin and

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**Table 1. Phase II trials: single-agent gemcitabine**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Patients (evaluable)</th>
<th>Gemcitabine (mg/m²)</th>
<th>Response rate (%)</th>
<th>Median survival time (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatzeimeir [12]</td>
<td>151</td>
<td>1,250</td>
<td>21.8</td>
<td>9.4</td>
</tr>
<tr>
<td>Abratt [13]</td>
<td>76</td>
<td>1,000-1,250</td>
<td>20</td>
<td>9.2</td>
</tr>
<tr>
<td>Anderson [14]</td>
<td>79</td>
<td>800-1,000</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>U.S. [15]</td>
<td>30</td>
<td>800</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Fukuoka [16]</td>
<td>73</td>
<td>1,000</td>
<td>26</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yokayama [17]</td>
<td>67</td>
<td>1,000</td>
<td>21</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
gemcitabine or possibly be related to their temporal relationship in that the nadir of thrombocytopenia for cisplatin occurs around day 15.

RESULTS OF RANDOMIZED PHASE III STUDIES

Gemcitabine versus Supportive Care

Anderson et al. reported on their trial of 299 symptomatic patients with advanced or metastatic NSCLC [28]. Patients were randomized to 1,000 mg/m² weekly times three of each four-week cycle or supportive care (i.e., palliative radiation and pain medications). The two arms were well balanced with respect to stage (~40% stage IV) and performance status (Karnofsky performance status [KPS] 60-70: ~30%; 80-90: ~70%). The primary endpoint was control of symptoms. Improvements were noted in terms of need for palliative radiotherapy at two months, 42.3% versus 7.3%, and in the median time to needing radiotherapy, 29.1 versus 3.8 weeks, p < 0.001, favoring the gemcitabine arm. There was also improvement in quality of life assessment for the gemcitabine treated patients at two and four months, 37% versus 35%, p = 0.048, and 44% versus 26%, p = 0.034, respectively. Improvements were also noted in the patient-assessed symptom scale, 33.3% versus 12.7%, p < 0.01. The overall response rate for gemcitabine was 17%. There was no difference in median survival, 24.4 weeks versus 25.5 weeks, respectively.

A similar study should be noted, which randomized 191 elderly patients (161 analyzed) (>70 years) with advanced NSCLC and ECOG performance status 0-2 to observation or vinorelbine 30 mg/m² days 1 and 8 every 21 days [29]. The results of this study revealed improvement in cancer-related symptoms as well as improvement in median survival (28 versus 21 weeks, p = 0.03). These studies support the concept that single-agent chemotherapy with gemcitabine or vinorelbine can provide meaningful benefit to patients with advanced NSCLC.

Single-Agent Gemcitabine versus Cisplatin/Etoposide

There have been two randomized phase II trials of single-agent gemcitabine versus the combination of cisplatin plus etoposide (PE) [30, 31]. Inclusion criteria were similar for both studies and included previously untreated patients with inoperable stage IIIa/b, and IV; Zubrod performance status of 0-2, and the absence of known brain metastases. In the Taiwanese study 50 patients were randomized to receive either gemcitabine 1,250 mg/m² weekly times three of each four-week cycle versus cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² i.v. days 1-3 of each four-week cycle [30]. Toxicities were generally mild and favored single-agent gemcitabine. Grade 3/4 thrombocytopenia was 7.4% and 7.7%, and grade 3/4 neutrophils was 57.7% and 52.5%, respectively. The incidence of febrile neutropenia was greater on the combination arm, 15.4% versus 0%. The incidence of red blood cell transfusions was greater on the combination arm, 15% versus 23%, respectively. Non-hematologic toxicity was mild and again favored the gemcitabine arm, with grade 3/4 nausea/vomiting occurring in 34.6% of patients on the combination arm versus 9.7% of patients treated with gemcitabine. There was no difference between the two arms in terms of response rates: 19% on the gemcitabine arm versus 21% for PE; time to progression 8.8 months versus 8.5 months, or median survival 37 weeks versus 48 weeks, respectively.

Manegold et al. reported on their study conducted in Europe of gemcitabine versus PE [31]. In this study 138

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Patients</th>
<th>Stage III/IV (%)</th>
<th>Grade 3/4 platelets</th>
<th>Grade 3/4 neutrophils</th>
<th>Response rate</th>
<th>Median survival time (mos.)</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandler [21]</td>
<td>27</td>
<td>17/83</td>
<td>50%</td>
<td>51%</td>
<td>33%</td>
<td>8.4</td>
<td>37%</td>
</tr>
<tr>
<td>Crino [22]</td>
<td>48</td>
<td>46/54</td>
<td>52%</td>
<td>36%</td>
<td>34%</td>
<td>15.4</td>
<td>59%</td>
</tr>
<tr>
<td>Abratt [23]</td>
<td>53</td>
<td>62/38</td>
<td>25%</td>
<td>57.7%</td>
<td>54%</td>
<td>13</td>
<td>61%</td>
</tr>
<tr>
<td>Steward [24]</td>
<td>60</td>
<td>68/32</td>
<td>27.1%</td>
<td>52.5%</td>
<td>52%</td>
<td>10.2</td>
<td>40%</td>
</tr>
<tr>
<td>Anton [25]</td>
<td>40</td>
<td>55/44</td>
<td>16%*</td>
<td>56%*</td>
<td>37%</td>
<td>10.4</td>
<td>35%</td>
</tr>
<tr>
<td>Shepherd [26]</td>
<td>38</td>
<td>18/82</td>
<td>21%</td>
<td>39%</td>
<td>47.5%</td>
<td>NA</td>
<td>NA%</td>
</tr>
<tr>
<td>Green [27]</td>
<td>48</td>
<td>15/85</td>
<td>28.6%</td>
<td>42.8%</td>
<td>32%</td>
<td>8.4</td>
<td>30%</td>
</tr>
</tbody>
</table>

*Described as % of cycles. NA = Not available.
patients with inoperable stage IIIa/b or IV NSCLC were randomized to receive gemcitabine 1,000 mg/m² weekly times three of each four-week cycle or cisplatin 100 mg/m² day 1 plus etoposide 100 mg/m² days 1-3 of each four-week cycle. Toxicities were mild and predominantly hematologic favoring the gemcitabine arm. Grade 4 neutropenia occurred in only 2% of gemcitabine patients as compared to 12% for patients treated with PE. There were no episodes of neutropenic fever on the gemcitabine arm versus 8% of patients on the PE arm. Red blood cell transfusions were given to 13% of patients on gemcitabine versus 23% of patients on PE. Grade 3/4 thrombocytopenia occurred in less than 3% of patients on each arm. Platelet transfusions were not required on either arm. There was no difference between the two arms in terms of response rates: 18.2% on the gemcitabine arm versus 15.3% for PE; time to progression 4.2 months versus 4.9 months, or median survival 6.6 months versus 7.6 months, respectively.

Randomized phase II studies must be interpreted with a degree of caution. By design, these trials attempt to discern differences in toxicity. The studies by Perng et al. and Manegold et al. reveal that patients treated with single-agent gemcitabine suffered with less myelosuppression and subsequently fewer episodes of neutropenic fever than those patients treated with PE. Fewer patients required transfusions with packed red blood cells, as well. With respect to non-hematologic toxicity, not surprisingly, there was a decreased incidence of significant nausea and/or vomiting seen in patients treated with gemcitabine.

These two trials were not powered statistically to discern small differences in survival, nor were they capable of proving equivalency between the two arms. In fact, equivalency studies require more patients than studies designed to reveal differences in survival.

Having said that, it is reasonable to conclude that single-agent gemcitabine is better tolerated than PE in untreated patients with advanced or metastatic NSCLC, with comparable survival data.

**Gemcitabine/Cisplatin versus Cisplatin/Etoposide**

(Tables 3 and 4)

A Spanish trial randomized 135 chemotherapy-naive patients with locally advanced or metastatic NSCLC to receive either cisplatin 100 mg/m² day 1 plus etoposide 100 mg/m² i.v. days 1-3 (PE) or cisplatin 100 mg/m² day 1 plus gemcitabine 1,250 mg/m² days 1 and 8 (PG) [32]. Both regimens were cycles repeated every 21 days [32] (Table 3, 4). Details are listed in Table 3, but both arms were well balanced with respect to age, gender, performance status (ECOG 0-2) and stage. The authors reported significant improvements favoring the gemcitabine plus cisplatin arm in terms of response rate: 40.6% versus 21.9%, \( p = 0.02 \), and time to progression, 6.9 versus 4.3 months, respectively, \( p = 0.01 \). There was a trend favoring the cisplatin plus gemcitabine arm in terms of survival: 8.7 versus 7.2 months, but given the small number of patients, this did not reach statistical significance (\( p = 0.18 \)). With respect to toxicity, there was an increased incidence of grade 4 neutropenia on the PE arm, 56% versus 28% (\( p = \)

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**Table 3. Phase III trials of the combination of gemcitabine plus cisplatin: patient characteristics**

<table>
<thead>
<tr>
<th>Spanish [32]</th>
<th>Italian [33]</th>
<th>International (Sandler et al.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gemcitabine + Cisplatin</td>
<td>Cisplatin + Etoposide</td>
</tr>
<tr>
<td>No. patients</td>
<td>69</td>
<td>66</td>
</tr>
<tr>
<td>M/F (%)</td>
<td>93/7</td>
<td>92/8</td>
</tr>
<tr>
<td>Age, median</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Stage (%)</td>
<td></td>
<td></td>
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<tr>
<td>IIIa</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIb</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>IV</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td><em>Performance status (%)</em></td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>70</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>80</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>90</td>
<td>20</td>
<td>15</td>
</tr>
</tbody>
</table>

*Karnofsky scale for Spanish and International trials; Zubrod performance scale for Italian trial. NA = not available.*
0.0009), with an increased incidence of neutropenic fevers, 7% versus 12%. Grade 4 thrombocytopenia was less frequent but occurred more commonly on the PG arm, 16% versus 5%. There were no serious hemorrhagic events on either arm.

The study by Cardenal et al. is another randomized phase II trial with the inherent deficiencies described earlier [32]. This trial compared the combination of cisplatin plus gemcitabine (CG) as a 21-day regimen with PE. As described earlier, CG, when administered as a 28-day regimen, exhibited a significant incidence of grade 3/4 thrombocytopenia, predominantly on day 15. This resulted in approximately 50% of patients requiring dose reductions or omissions of their day 15 gemcitabine. Cardenal’s regimen utilized a 21-day cycle with cisplatin on day 1 and gemcitabine 1,250 mg/m² on days 1 and 8. Given the increased dose of gemcitabine and the 21-day cycle, the expected dose intensity for gemcitabine was actually greater (833 mg/m²/week versus 750 mg/m²/week).

With respect to the hematological toxicity, there was an increased incidence of grade 4 neutropenia seen in patients treated with PE as well as an increased incidence of neutropenic fevers. Grade 4 thrombocytopenia was again greater on the CG arm, but the incidence was lower than that seen in the trials employing the 28-day cycle. Response rate, time to progression, and survival favored the CG arm, with response rate and time to progression reaching statistical significance. Thus, it would appear that the combination of CG utilizing a 21-day cycle compares favorably to PE in terms of toxicity, response and survival.

**Gemcitabine/Cisplatin versus Mitomycin/Ifosfamide/Cisplatin (Tables 3 and 4)**

The Italian Lung Cancer project reported on the results of their randomized phase III trial in patients with chemotherapy-naïve advanced or metastatic NSCLC [33]. From January 1996 through February 1997, 307 patients were randomized to either mitomycin 6 mg/m² day 1, ifosfamide 3 gm/m² day 1 and cisplatin 100 mg/m² day 2 (MIC) or cisplatin 100 mg/m² day 2 plus gemcitabine 1,000 mg/m² days 1, 8, and 15 (GC). Both regimens were repeated every 28 days. Patient characteristics included performance status (ECOG 0-2), previously treated brain metastases, and only stage IIIb with either supravacicular lymph nodes or malignant pleural effusions were included. Patient characteristics were similar for both treatment arms. Response rate favored the cisplatin/gemcitabine arm: 38% versus 26%, \( p = 0.03 \). There was no difference in median survival: 8.6 months versus 8.8 months, respectively, \( p = NS \). Toxicity was principally hematologic with grade 3/4 thrombocytopenia and neutropenia occurring in 48% versus 26% in GC and MIC, respectively. Nonhematologic toxicity was mild and consisted of nausea/vomiting (18% versus 23%) and alopecia (12% versus 39%).

**Gemcitabine/Cisplatin versus Cisplatin (Tables 3 and 4)**

Sandler et al. reported on the results of an international randomized phase III study of gemcitabine and cisplatin versus cisplatin alone in chemotherapy-naïve patients with advanced or metastatic NSCLC (Sandler et al., unpublished data). Patients were randomized to receive either cisplatin 100 mg/m² i.v. on day 1 of a 28-day cycle, or the combination of cisplatin 100 mg/m² i.v. on day 1 plus gemcitabine 1,000 mg/m² administered i.v. on days 1, 8, and 15 of a 28-day cycle. Patient characteristics included KPS of 70-100, stage IIIa–IV. Patients with central nervous system metastases were not eligible. Patient characteristics were evenly matched between the two treatment arms. Nonhematologic toxicity was mild. Hematologic toxicity was more pronounced in the combination arm, with grade 3/4 neutropenia occurring in 21.7%/35.3% of patients as compared to 3.3%/1.2% on the
cisplatin arm. The incidence of neutropenic fevers was less than 5% in either arm. Grade 3/4 thrombocytopenia occurred in 25%/25.4% of patients on the combination arm versus 2.8%/0.8% of patients on the cisplatin arm. There were no serious hemorrhagic events related to thrombocytopenia in either arm. There was a significant improvement with regard to response rate, 30.4% versus 11.1%, \( p < 0.0001 \); median time to progressive disease 5.6 versus 3.7 months, \( p = 0.0013 \), and overall survival 9.1 versus 7.6 months, \( p = 0.004 \) favoring the combination of gemcitabine plus cisplatin.

The results of these randomized trials would support the statement that the combination of monthly cisplatin with gemcitabine is an active regimen in NSCLC and in at least one trial revealed a significant survival advantage when compared to standard therapy. This combination should now be considered for use as front-line therapy in patients with advanced or metastatic NSCLC.

**NON-CISPLATIN CONTAINING DOUBLET COMBINATIONS**

**Combination Phase II Studies - Carboplatin (Table 5)**

Gemcitabine has been used in combination with another platinum analogue, carboplatin. *Carmichael et al.* reported on a phase I/II trial of weekly gemcitabine at a fixed dose of 1,000 mg/m\(^2\) on days 1, 8, and 15 [34]. Carboplatin was dosed using the Calvert formula and administered immediately before gemcitabine on day 1. Carboplatin AUCs were 4 and 5.2. The maximum tolerated dose for carboplatin was AUC of 5.2. Grade 3/4 thrombocytopenia was dose-limiting, occurring in 43.7% of patients. Grade 3/4 neutropenia occurred in 50% of patients. Responses were seen in 4 of 13 patients (31%) treated at both carboplatin dose levels. The median survival was 45 weeks. In order to assess the effect of sequencing the same doses of each agent were utilized with gemcitabine administered before carboplatin. No difference in toxicity was noted and response rate was not commented upon. *Ng et al.* reported on a Hoosier Oncology study using the same dosing schema as *Carmichael*, with carboplatin administered after the gemcitabine on day 1 [35]. Seven patients were entered, with five evaluable for toxicity. Grade 3/4 thrombocytopenia occurred in four patients (10, 12, 27, and 38 \( \times 10^9/\text{l} \)) and the study was terminated due to excessive toxicity. There were no responses seen. It should not be surprising to see the degree of thrombocytopenia on day 15 with these regimens given the incidence of thrombocytopenia seen with cisplatin plus gemcitabine in the four-week regimen. The primary toxicity of carboplatin is myelosuppression and thrombocytopenia that typically occur around day 15.

Two groups of investigators have attempted to abrogate the thrombocytopenia by either dosing the carboplatin on day 8 of a 28-day regimen or truncating the regimen to a 21-day cycle, with carboplatin administered on day 1 and gemcitabine on days 1 and 8 [36, 37]. *Martinez et al.* reported the results of their phase I/II study of chemotherapy-naïve patients with advanced NSCLC treated with carboplatin day 1 and gemcitabine days 1 and 8 [36]. Cycles were repeated every 21 days. The maximum tolerated dose has not yet been reached with patients currently accruing to gemcitabine 1,200 mg/m\(^2\) and carboplatin AUC 5.2. *Iaffaioli et al.* reported on their phase I/II study of chemotherapy-naïve patients with advanced NSCLC treated with gemcitabine on days 1 and 8 plus carboplatin on day 8 [37]. The maximum tolerated dose was gemcitabine 1,000 mg/m\(^2\) and carboplatin AUC 5. Neutropenia was dose-limiting, with three of five patients experiencing grade 4 neutropenia at gemcitabine 1,200 mg/m\(^2\) and carboplatin AUC 5. Overall, responses were seen in 13/26 patients (50%), with a median survival of 16 months.

<table>
<thead>
<tr>
<th>Author</th>
<th>Carboplatin</th>
<th>Gemcitabine mg/m(^2)</th>
<th>Prior Tx</th>
<th>No. patients</th>
<th>Response rate (%)</th>
<th>Median survival time (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Carmichael</em> [34]</td>
<td>5.2 (MTD) day 1</td>
<td>1,000 days 1, 8, 15 q 4 weeks</td>
<td>No</td>
<td>13</td>
<td>31</td>
<td>11.2</td>
</tr>
<tr>
<td><em>Ng</em> [35]</td>
<td>AUC = 5 day 1</td>
<td>1,000 days 1, 8, 15 q 4 weeks</td>
<td>No</td>
<td>7</td>
<td>0</td>
<td>4.3</td>
</tr>
<tr>
<td><em>Martinez</em> [36]</td>
<td>AUC = 4 – 5.2 day 1</td>
<td>800 – 1,200 days 1, 8 q 3 weeks</td>
<td>No</td>
<td>12</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><em>Iaffaioli</em> [37]</td>
<td>AUC = 5 day 8</td>
<td>800 – 1,200 days 1, 8 q 28 days</td>
<td>No</td>
<td>26</td>
<td>50</td>
<td>16</td>
</tr>
</tbody>
</table>

*Recommended phase II dose: Carboplatin AUC = 5 plus gemcitabine 1,100 mg/m\(^2\) days 1 and 8 of each 28-day cycle. NR = not reported.*
Given the results of the randomized trials that have clearly established gemcitabine as an active agent in NSCLC, another logical step is to look into gemcitabine in combination with active agents other than cisplatin. Toward this end, several investigators have conducted trials combining gemcitabine with a variety of agents (i.e., taxanes, vinorelbine, CPT-11, and ifosfamide). Herein, I will describe the results of six such trials evaluating the combination of gemcitabine with either paclitaxel or docetaxel [38-43]. Two studies have combined gemcitabine administered on days 1 and 8 with paclitaxel on day 1 of a 21-day cycle. [38, 39]. Paclitaxel doses ranged from 150 to 200 mg/m$^2$ over three hours, with gemcitabine 900 to 1,000 mg/m$^2$.

Georgoulias et al. [38] treated 50 patients with NSCLC previously exposed to chemotherapy and noted a response rate of 22%, with a median survival of 14 months [38]. The authors noted mild hematologic toxicity (grade 3/4 neutropenia 12%, grade 4 thrombocytopenia 2%). Grade 2/3 neurotoxicity occurred in 32% of patients and grade 2/3 asthenia in 52%. Grade 2/3 asthenia and flu-like symptoms were noted in 30% to 50% of patients in this phase I study. Two other studies utilized a three-week cycle with docetaxel on day 8 and gemcitabine on days 1 and 8 [42, 43]. Docetaxel doses were 75 to 100 mg/m$^2$ and gemcitabine doses 800 to 1,000 mg/m$^2$. Response rates of 37.5% [42] and 44% [43] were reported in these two trials. Georgoulias et al. reported grade 4 neutropenia in 40% of patients with only 3 episodes of neutropenic fever [40]. Grade 3/4 thrombocytopenia was reported in 23% of patients. Grade 2/3 asthenia and flu-like symptoms were noted in 30% to 50% of patients in this phase I study. Two other studies utilized a three-week cycle with docetaxel on day 8 and gemcitabine on days 1 and 8 [42, 43]. Docetaxel doses were 75 to 100 mg/m$^2$ and gemcitabine doses 800 to 1,000 mg/m$^2$. Response rates of 37.5% [42] and 44% [43] were reported in these two trials. Georgoulias et al. reported grade 3/4 neutropenia in 8% of patients, all complicated with a febrile episode [42]. Grade 4 thrombocytopenia occurred in only 2% of patients. Grade 2/3 neurotoxicity and asthenia occurred in 8% and 20% of patients, respectively.

Gemcitabine plus Vinorelbine (Table 7)

Five phase I or II studies have recently evaluated the combination of gemcitabine plus vinorelbine [44-48]. Three studies utilized a three-week cycle with gemcitabine and vinorelbine administered on days 1 and 8 [44-46]. Recommended phase II doses for vinorelbine ranged from 25 to 30 mg/m$^2$ and for gemcitabine 1,000 to 1,250 mg/m$^2$. Response rates of 25% to 30% were observed. Grade 3/4 neutropenia occurred in 55%. Grade 4 thrombocytopenia was primarily hematologic.

Others (CPT-11, Ifosfamide)

Gemcitabine has also been combined with the alkylating agent ifosfamide, as well as the topoisomerase I inhibitor CPT-11 [49, 50]. Manegold et al. reported on a phase II trial of a fixed schedule of weekly gemcitabine 1,000 mg/m$^2$ on days 1, 8, and 15 with ifosfamide [49]. Ifosfamide was dosed on a...
daily times five schedule on days 8 through 12 at a dose of 1,500 mg/m². Cycles were repeated every four weeks. A total of 56 patients with previously untreated advanced NSCLC were entered onto this trial, of whom 50 patients were evaluable for response. Responses were seen in 16 of 50 patients for a response rate of 32%.

Rocha Lima et al. reported on their ongoing phase I trial of gemcitabine plus CPT-11 [50]. The gemcitabine dose was fixed at 1,000 mg/m², with escalating doses of CPT-11 starting at 50 mg/m². Each agent was administered on days 1 and 8 of each 21-day cycle. Patients have completed cohort 3 with a CPT-11 dose of 100 mg/m². Further CPT-11 dose escalation is ongoing.

**Triplet Combinations**

The next concept to study is whether adding a third drug in combination provides an increase in activity without excessive toxicity. As such, gemcitabine has been studied in a number of three-drug combinations.

**Gemcitabine plus Paclitaxel plus Carboplatin or Cisplatin (Table 8)**

There have been four studies combining gemcitabine plus paclitaxel plus either carboplatin or cisplatin [51-54]. Details are listed in Table 8. Response rates ranged from 29% to 52%, with neutropenia and neutropenic fevers being the most common toxicities noted. In the largest phase II trial of 63 patients treated with the combination of paclitaxel plus carboplatin plus gemcitabine, Hainsworth et al. reported grade 3/4 leukopenia and thrombocytopenia in 51% and 43% of patients, respectively. Fifteen patients suffered with neutropenic fevers [51]. The incidence of grade 3/4 fatigue and neuropathy was 12% and 7%, respectively.

**Gemcitabine plus Vinorelbine plus Cisplatin, Ifosfamide or Mitomycin (Table 9)**

Several other triplet combinations are listed in Table 9 [55-59]. These combinations appear interesting, with response rates ranging from 33% to 52% in studies involving small numbers of patients. Again, myelosuppression is the most common toxicity.

The concept of triplet combination chemotherapy will not be answered in the context of small, limited institutional phase II trials. This will only be answered with randomized phase III trials that compare the three-drug combination to a similar two-drug combination without gemcitabine (i.e., paclitaxel plus carboplatin with/without gemcitabine).

**Gemcitabine plus Radiation Therapy**

Gemcitabine is known to be a potent radiation sensitizer. The results of a recent phase II trial conducted in Europe attest to its potency clinically and provide a warning for future trials. Scalliet et al. report on a trial conducted from October 1994 through August 1995. Gemcitabine 1,000 mg/m² was administered weekly times six weeks along with thoracic radiotherapy 2 Gy/fraction, daily times five/week for six weeks (60 Gy) [60]. Eight patients were enrolled but the study was terminated due to excessive toxicity. There were three treatment-related deaths. Two deaths were due to pulmonary toxicity and one hemorrhage secondary to radiation necrosis. Three patients suffered complications due to acute radiation toxicity (pneumonitis and esophagitis). Further studies are being conducted utilizing phase I dose escalation of gemcitabine with concurrent radiotherapy. The Cancer and Leukemia Group B has recently completed a three-arm phase II trial of induction
chemotherapy followed by concurrent chemotherapy with thoracic radiotherapy [61]. All patients receive four cycles of cisplatin 80 mg/m² every 21 days. Radiotherapy is initiated on day 43 (cycle 3) at 200 cGy/day (5×/week) to a total dose of 6,600 cGy. The other chemotherapy agents include arm 1: gemcitabine 1,250 mg/m² on days 1, 8, 22, and 29, and 600 mg/m² on days 43, 50, 64, and 71; arm 2: paclitaxel 225 mg/m² over 3 h on days 1 and 22, and 135 mg/m² on days 43 and 64; arm 3: vinorelbine 25 mg/m² on days 1, 8, 15, 22, and 29, and 15 mg/m² on days 43, 50, 57, 64, and 71. Preliminary analysis (12 patients on each arm) revealed grade 3/4 toxicities for the concurrent radiotherapy and gemcitabine plus cisplatin arm to be thrombocytopenia (40%/30%), neutropenia (20%/20%) and esophagitis (40%/10%). It would appear that lower-dose gemcitabine may be given concurrently with radiotherapy, but should be reserved for controlled clinical trials at this time.

**SUMMARY**

In summary, it would appear that gemcitabine clearly has activity as a single agent in advanced NSCLC. Given the results of three randomized trials, the combination of gemcitabine plus cisplatin should be considered one of the more effective combinations in advanced NSCLC. This combination should be evaluated in earlier-stage disease (i.e., adjuvant surgical trials) to see if the modest impact on survival in patients with metastatic disease may translate into improvement in long-term survival in patients with potentially curable disease. Further studies looking at

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### Table 8. Phase I or II trials: three-drug combinations: gemcitabine plus paclitaxel plus cisplatin or carboplatin

<table>
<thead>
<tr>
<th>Author</th>
<th>Paclitaxel (mg/m²)</th>
<th>Carboplatin (AUC)</th>
<th>Gemcitabine (mg/m²)</th>
<th>No. Patients</th>
<th>Response rate (%)</th>
<th>Median survival time (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Hainsworth</em> [51]</td>
<td>200 (1) day 1</td>
<td>AUC = 5 day 1</td>
<td>1,000 days 1, 8 q 3 weeks</td>
<td>63</td>
<td>48</td>
<td>NR</td>
</tr>
<tr>
<td><em>Kelly</em> [52]</td>
<td>175 (3) day 1</td>
<td>AUC = 6→5 day 1</td>
<td>600–1,000 days 1, 8 q 3 weeks</td>
<td>21</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td><em>Frasci</em> [53]</td>
<td>150+ (1) day 1</td>
<td>50 mg/m² day 1, 8</td>
<td>1,000 days 1, 8 q 3 weeks</td>
<td>26</td>
<td>3/10 pre-tx</td>
<td>9/16 no-tx</td>
</tr>
<tr>
<td>Sorensen [54]</td>
<td>110 (3) q other wk</td>
<td>60 mg/m² q other wk</td>
<td>800 mg/m² q other wk</td>
<td>33</td>
<td>52</td>
<td>NR</td>
</tr>
</tbody>
</table>

Recommended phase II dose: Paclitaxel 175 mg/m² plus carboplatin AUC = 5 plus gemcitabine 1,000 mg/m² days 1, 8.

# Includes previously treated patients. NR = not reported.

### Table 9. Phase I/II three-drug combinations: gemcitabine plus other agents

<table>
<thead>
<tr>
<th>Author</th>
<th>Other (mg/m²)</th>
<th>Other (mg/m²)</th>
<th>Gemcitabine (mg/m²)</th>
<th>No. patients</th>
<th>Response rate (%)</th>
<th>Median survival time (mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzalez-Baron [55]</td>
<td>Vinorelbine 30 days 1, 8</td>
<td>Cisplatin 100 day 1</td>
<td>1,000 days 1, 15 q 28 days</td>
<td>61</td>
<td>46</td>
<td>NA</td>
</tr>
<tr>
<td>Dorta [56]</td>
<td>Vinorelbine 25 days 1, 8, 15</td>
<td>Cisplatin 30 days 1, 8, 15</td>
<td>800 days 1, 8, 15 q 28 days</td>
<td>43</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td>Catellano [57]</td>
<td>Ifosfamide 3 g/m² day 1</td>
<td>Vinorelbine 25 days 1, 8</td>
<td>1,000–1,250 days 1, 8 q 21 days</td>
<td>21</td>
<td>52</td>
<td>NA</td>
</tr>
<tr>
<td>Boni [58]</td>
<td>Ifosfamide 2 g/m² day 1</td>
<td>Cisplatin 80 day 2</td>
<td>1,000 days 1, 8 q 21 days</td>
<td>47</td>
<td>4/13 pre-tx</td>
<td>20/34 no-tx</td>
</tr>
<tr>
<td>Gralla [59]</td>
<td>*Vinorelbine 30 q wk</td>
<td>Mitomycin 8 days 1, 29, 71, 113</td>
<td>#600–1,000 q wk</td>
<td>20</td>
<td>45</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Vinorelbine administered weekly times 5, then every other week with half doses on “off weeks.”

#Gemcitabine administered weekly times 5, then every other week. NA = not available.
novel non-cisplatin-based combinations with gemcitabine appear promising and will be worthy of continued study. Only phase III trials will be able to confirm this promise of activity and tolerability. Gemcitabine is a potent radiation sensitizer and its role will be further defined in ongoing controlled clinical trials.

REFERENCES


