Review

The role of single-agent gemcitabine in the treatment of non-small-cell lung cancer

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Summary

Gemcitabine is a novel antimetabolite which has shown antitumor activity against a variety of tumors including non-small-cell lung cancer (NSCLC). Phase I clinical trials with gemcitabine revealed it was well tolerated and several phase II trials were conducted. This report will summarize the data from 15 phase I–II trials conducted in both untreated and treated patients with advanced lung cancer. Overall, single-agent gemcitabine was active with response rates in untreated patients ranging from 14%-33% and 0%-25% in previously treated patients. Grade 4 toxicities were infrequent with neutropenia reported in 2%-6% of patients and grade 4 thrombocytopenia was rare (1%). One randomized phase III trial comparing the efficacy and safety of gemcitabine to best supportive care confirmed the role of gemcitabine as an active agent for the treatment of NSCLC. Furthermore, gemcitabine was shown in several economic models to be cost-effective. In summary single agent gemcitabine is active, minimally toxic, and cost-effective as a treatment regimen for patients with advanced lung cancer. Studies combining gemcitabine with other active agents are underway and have reported promising results. As monotherapy, gemcitabine may make a valuable contribution to those patients with a poor performance status or comorbid diseases desiring treatment studies in this setting should also be considered.

Key words: gemcitabine, non-small-cell lung cancer

Introduction

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer deaths for men and women in the US and is a significant cause of cancer death across the world [1]. A major factor contributing to this high mortality rate is the advanced stage of disease present at the time of diagnosis for which we have no effective treatment. However, recent data suggests that while cisplatin-based chemotherapy in advanced disease does not cure patients it does provide a short term survival benefit and palliates symptoms with improvement in quality of life [2–7]. These positive effects from chemotherapy suggest that discovering more efficacious agents would be worthwhile. In recent years several new chemotherapy agents have been identified, each of which produces higher response rates and longer survival than older single agents such as cisplatin [8].

One of these new chemotherapy agents is a novel antimetabolite, gemcitabine. Although previous antimetabolites had little activity in NSCLC, gemcitabine was developed because of its prolonged retention time in tumor cells as compared to other antimetabolites and its high rate of antitumor activity against solid tumors in vitro and in vivo [9, 10]. Gemcitabine is a deoxycytidine analogue. After cellular uptake gemcitabine is phosphorylated to gemcitabine di- and triphosphates, the active metabolites [11, 12]. The primary mechanism of action is gemcitabine triphosphate ability to halt DNA synthesis by competing with the natural nucleotide, deoxycytidine triphosphate (dCTP) for incorporation into the replicating DNA strand causing DNA fragmentation and cell death [11, 12]. This effect is enhanced by a number of unique self-potentiating mechanisms of the active metabolites which results in maintaining high intracellular concentrations of the active metabolites and increases the probability for gemcitabine triphosphate to be incorporated into the DNA. Finally, once gemcitabine is incorporated into the DNA chain its position is hidden from DNA repair enzymes that might otherwise want to repair the DNA abnormality. Gemcitabine is active against human tumor xenograft models of carcinoma from the pancreas, lung, breast, ovary, sarcoma, and head and neck [9]. In murine models of NSCLC xenografts, gemcitabine given at the maximally tolerated dose inhibited tumor growth by 45%-76%, as compared to control animals [13].

Initially four dose schedules of gemcitabine were evaluated but three were discontinued due to schedule-dependent toxicity [14–18]. The recommended dose and schedule for phase II trials was 800 mg/m² weekly times three with a one week rest period. Utilizing this schedule in heavily pretreated patients revealed thrombocytopenia to be dose limiting but significant myelosuppression was minimal. Non-hematological toxicities were mild and included nausea, vomiting, anorexia, malaise, transient elevation of transaminases, flu-like syndrome, skin rashes and renal dysfunction.
weekly schedule versus Grade 3 or 4 liver abnormalities were also slightly
bocytopenia developed in 26% of patients on the twice weekly schedule (19% vs. 21%, respectively) but was more toxic.
The investigators compared their twice weekly schedule to their weekly schedule and found grade 3 or 4 thrombocytopenia in 2%-6% of patients and rare neutropenia in 15% of patients on the PE arm.

However, when gemcitabine was given on a twice weekly schedule the response rate was similar to the weekly schedule (19% vs. 21%, respectively) but was more toxic. The investigators compared their twice weekly schedule to their weekly schedule and found grade 3 or 4 thrombocytopenia developed in 26% of patients on the twice weekly schedule versus 5% on a weekly schedule [29].

Grade 3 or 4 liver abnormalities were also slightly increased in the twice weekly study 12% for ALT and 13% AST versus 9% and 7%, respectively, for the patients on the weekly schedule. There was greater nausea and vomiting and peripheral edema observed in patients receiving the twice weekly schedule. Most concerning was 64% of patients on the alternative schedule developed a flu-like syndrome versus 19% of patients receiving standard treatment.

Two randomized phase II trials comparing single-agent gemcitabine to cisplatin plus etoposide (PE) have been completed (Table 2) [30, 31]. The two trials differed slightly in their designs. Manegold gave gemcitabine at 1000 mg/two-weekly on days 1, 8, and 15 of a four-week cycle and cisplatin at 100 mg/m² on day 1 with etoposide at 100 mg/m² every four weeks [30]. Perng administered 1250 mg/m² of gemcitabine weekly for three weeks every 28 days and cisplatin at 80 mg/m² on day 1 with etoposide at 80 mg/m² on days 1–3 every four weeks [31]. The response rate for gemcitabine was 18% and 19% and was similar to the response rate for the PE combination (15% and 21%). The response rate in the gemcitabine arms compares favorably to the response rates observed in the nonrandomized phase II trials reported above. There was no difference in time to progression or survival between the gemcitabine and PE arms. Not surprisingly, gemcitabine had fewer toxicities than the combination with the most frequent toxicity being nausea and vomiting and alopecia with the cisplatin and etoposide regimen. Hematological toxicity was also more severe for the combination. Perng reported febrile neutropenia in 15% of patients on the PE arm versus 0% of patients on the gemcitabine arm while Manegold observed grade 3 or 4 neutropenia in 15% of patients receiving PE versus 7% of patients given gemcitabine. Quality of life analysis favored single-agent gemcitabine. Based on these studies, single-agent gemcitabine may be preferred over the prior standard combination.

To address the question of the optimal dose of gemcitabine to be delivered, a randomized double-blinded phase II study comparing two doses of gemcitabine has

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose (mg/m²)</th>
<th>Number of evaluable patients</th>
<th>RR (%)</th>
<th>MS (mos)</th>
<th>Percentage grade 3-4</th>
<th>ANC (%)</th>
<th>Pits (%)</th>
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<tbody>
<tr>
<td>Abratt [19]</td>
<td>1000-1250</td>
<td>76</td>
<td>20</td>
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<tr>
<td>Anderson [20]</td>
<td>800-1000</td>
<td>79</td>
<td>20</td>
<td>7</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Begbie [21]</td>
<td>1250</td>
<td>29</td>
<td>21</td>
<td>7.5</td>
<td>NR</td>
<td>NR</td>
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<td>Fossella [22]</td>
<td>1000-2800</td>
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<td>25</td>
<td>12.3</td>
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<td>Fukuoka [23]</td>
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<td>Gatzemeier [24]</td>
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<tr>
<td>Lund [25]</td>
<td>90</td>
<td>81</td>
<td>19</td>
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<td>Malayeri [26]</td>
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<tr>
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<td>Alcedo [28]</td>
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<td>&lt;2</td>
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</table>

Abbreviations: RR - response rate; MS - median survival; ANC - patients with neutropenia; Pits - patients with thrombocytopenia; NR - not reported.

* Twice/week.

Table 1. Phase II clinical trials of gemcitabine in advanced NSCLC.

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose (mg/m²)</th>
<th>Number of evaluable patients</th>
<th>RR (%)</th>
<th>MS (mos)</th>
<th>Percentage grade 3-4</th>
<th>ANC (%)</th>
<th>Pits (%)</th>
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<tr>
<td>Perng [31]</td>
<td>Pe</td>
<td>Gemcita-</td>
<td>PE</td>
<td>18</td>
<td>15</td>
<td>19</td>
<td>21</td>
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<td>Median survival (months)</td>
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<td>7.6</td>
<td>9.3</td>
<td>12</td>
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<td>29</td>
<td>4</td>
<td>35</td>
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<td>0</td>
<td>4</td>
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<tr>
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<td>NR</td>
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<td>31</td>
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<td>15</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<td>15</td>
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<tr>
<td>Grade 3-4 thrombocytopenia (%)</td>
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<td>0</td>
<td>7</td>
<td>7</td>
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</table>

Abbreviations: PE - cisplatin and etoposide; TTP - time to progression; NR - not reported.

Table 2. Randomized phase II trials of gemcitabine versus cisplatin–etoposide.
been conducted [32]. Eighty-two chemonaive patients with advanced NSCLC were treated with 1250 mg/m² or 2500 mg/m² of gemcitabine on day 1, 8, and 15 of a 28-day schedule. Results for each arm are not available but overall toxicity has been mild with only four patients (5%) experiencing grade 4 toxicity. With a median follow-up of nine months 51% of the patients are alive.

Limited data for the role of gemcitabine as second-line therapy is available as depicted in Table 3 [33–35]. Two single institution trials reported a 21% and 25% response rate while no responses were seen for the same dose schedule in the multi-institutional randomized trial and only one patient (6%) responded in the high-dose arm of this study. Significant toxicity was infrequent in all studies although the high-dose arm reported five patients (31%) with grade 3 uncomplicated neutopenia.

One randomized phase III trial has been performed in the UK comparing gemcitabine to best supportive care in patients with advanced lung cancer [36]. Three hundred patients were randomized to gemcitabine 1000 mg/m² every week for three weeks out of four or best supportive care measures. An interim analysis revealed that 42% of patients on the best supportive care arm required radiotherapy within the first two months of the study as compared to only 7% in the gemcitabine arm. The response rate to gemcitabine was 17%. No survival data has been reported. Toxicity was mild with grade 3–4 neutropenia occurring in 13% of patients and grade 3–4 thrombocytopenia in 2% of patients. The most frequent nonhematological toxicity was grade 3 nausea and vomiting which developed in 9% of patients. Thus, this trial confirms the efficacy and safety of gemcitabine in advanced lung cancer.

Gemcitabine is also cost effective. Copley-Merriman performed a cost analysis using three different economic models in which gemcitabine was compared to cisplatin plus etoposide (two models) or ifosfamide and etoposide in patients with advanced non-small-cell lung cancer [37]. Single-agent gemcitabine provided a cost savings in all models. The combination regimens were more expensive because of hospitalization for chemotherapy administration and treatment for nausea/vomiting and febrile neutropenia. A Canadian economic model compared gemcitabine to best supportive care and concluded gemcitabine was a cost-effective intervention for the treatment of advanced lung cancer [38].

In summary, gemcitabine is active in non-small-cell lung cancer with minimal toxicity and acceptable cost. The recommended dose is 1000 mg/m² weekly for three out of four weeks. Gemcitabine's antitumor activity, palliative benefit and low toxicity profile makes it an ideal agent for combining with other active compounds. Numerous combination trials with the platinum agents, as well as the taxanes and vinorelbine are ongoing. As monotherapy in NSCLC gemcitabine may make an important contribution to those patients with poor performance status or patients with comorbid diseases desiring treatment. Studies in this setting are clearly warranted.

**References**