review

Gemcitabine and radiation therapy in non-small cell lung cancer: state of the art

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Stage III non-small cell lung cancer (NSCLC) treatment is evolving. There are several choices available regarding which chemotherapy to use and how to optimally combine them with radiotherapy. Gemcitabine (Gemzar®, Eli Lilly and Company, Indianapolis, USA) is a chemotherapeutic agent with activity in NSCLC, and preclinical studies have shown that gemcitabine is a potent radiosensitizer. These two characteristics make gemcitabine a potential option when treating patients with stage III NSCLC. This review article describes the efficacy and tolerance of gemcitabine when combined with radiation in those patients. Gemcitabine used concurrently with radiation, as an induction regimen before radiation, and as a consolidation regimen after radiation is reviewed.

Key words: gemcitabine, radiotherapy, chemotherapy, chemoradiation, non-small cell lung cancer

introduction

The treatment of stage III non-small cell lung cancer (NSCLC) is based on local and systemic control of the disease [1]. Chemotherapy has an obvious role in systemic control; however, it can also lend a hand in local control. Many chemotherapeutic agents have been shown to radiosensitize tumor cells or enhance the local effects of radiation.

Over the years, the treatment modality has evolved from radiation alone to using a cisplatin-based regimen prior to radiation to using a cisplatin-based regimen concurrently with radiation [1]. As our knowledge has increased on how to deliver radiation more effectively and safely, investigators are determining how to optimally use chemotherapy in conjunction with radiation.

The approval of newer generation drugs has further widened the scope of available options. Several large randomized phase III studies were conducted to determine the best drug combination for advanced stage NSCLC [2, 3]. The results of these studies have shown that most platinum-based combinations are comparable in terms of efficacy with similar median and 1-year survival times. Because of this plateau in survival, investigators are incorporating other treatment modalities in the hope of improving outcomes; however, with radiation, questions remain about the order in which chemotherapy and radiation should be given and which chemotherapy should be used.

gemcitabine and radiation therapy

Gemcitabine is one of the newer generation compounds that has shown activity in phase II trials in NSCLC as both a single agent [4] and in combination with other cytotoxic agents [2, 5, 6]. Several phase III studies have confirmed the efficacy of gemcitabine in stage IV NSCLC [7].

Preclinical data have shown that gemcitabine is a potent radiosensitizer. The mechanism by which gemcitabine causes radiation enhancement is not completely understood, but it is likely that several mechanisms play a part in the radiation-enhancing effects of the drug. These include depletion of dATP pools after gemcitabine administration, elimination of the radio resistant S-phase cells and redistribution of surviving cells into a more sensitive component, lowering of the radiation-induced apoptotic threshold, and/or oxygenation of tissue from shrinking tumor cells [8–10].

The timing of gemcitabine administration and radiation is important for the optimization of radiosensitization. An in vitro study by Huang and Hittelman was aimed at finding the duration of gemcitabine-induced radiosensitization, and chromosome repair was altered for 24 to 48 h following drug administration [11]. The effects of gemcitabine-mediated radiation sensitization can be expected to last 24 to 72 h.

The scheduling of gemcitabine administration and radiation is also important for the optimization of radiosensitization. Two preclinical studies compared weekly with twice-weekly gemcitabine. Mason et al. studied daily, twice-weekly, and weekly gemcitabine followed by radiation in a murine sarcoma model. All three schedules had equivalent enhancement of radiation; however, only the weekly schedule resulted in a slight protection of jejunal stem cells [10]. Fields et al. evaluated weekly and twice-weekly gemcitabine given with daily radiation...
in a murine head and neck squamous cell carcinoma model. The twice-weekly schedule was found to have a higher therapeutic index compared to the weekly schedule [12].

**gemcitabine given concurrently with radiation**

On the basis of preclinical and clinical studies, it is expected that gemcitabine given concurrently with radiation may produce radiation enhancement; however, the initial study of gemcitabine with concurrent radiation [13] ended with undesirable results due to multiple factors. It was originally hypothesized that since gemcitabine and 5-fluorouracil (5-FU) are structurally similar, they would react to radiation in a similar manner; therefore, a phase I dose-finding study was not completed for gemcitabine because full-dose 5-FU showed no excessive toxicity when it was combined with radiation. In the initial study, eight patients with stage IIIa/IIIb NSCLC received full-dose gemcitabine (1000 mg/m²) with 60 Gy of radiation in large treatment volumes (according to the Radiation Therapy Oncology Group [RTOG] guidelines at the time). The results were intriguing: seven of the eight patients (87%) responded at the primary tumor, and four of five patients (80%) responded at nodal sites. The toxicity, however, was unacceptable: three patients had treatment-related deaths (two from pulmonary toxicity, 1 from hemorrhage), three patients had complications due to acute radiation toxicity (pneumonitis or severe esophagitis), and another two had other serious side effects.

Based on the experience of this trial, several guidelines were formulated for the concurrent use of gemcitabine with radiation. First, the gemcitabine dose must be reduced. In subsequent studies, investigators gave gemcitabine at weekly doses ranging from 150 to 300 mg/m² (or twice-weekly at 35 mg/m²) with concurrent total doses of radiation up to 63 Gy without unexpected toxicities. Second, the radiation treatment field needs to be minimized. The 3-dimensional (3D) conformal radiation should be used whenever possible. Also, the planning treatment volume (PTV) should be less than 2000 cm³.

Weekly gemcitabine in combination with daily radiation is among the better studied regimens. In phase II evaluation, the gemcitabine dose ranged from 125 mg/m² to 600 mg/m², and the radiation dose used in the majority of studies was 1.8 to 2.0 Gy/day (Table 1). Gemcitabine in combination with platinum agents has also been evaluated (Table 1).

The Cancer and Leukemia Group B (CALGB) study 9431 [14] was a three-arm phase II study evaluating chemotherapy induction followed by concurrent chemoradiotherapy. The three arms were gemcitabine and cisplatin (arm 1), paclitaxel and cisplatin (arm 2), and vinorelbine and cisplatin (arm 3). The induction phase used full doses of each regimen followed by modified doses in the concurrent phase. In arm 1, the induction phase used gemcitabine 1250 mg/m² on days 1 and 8 with cisplatin 80 mg/m² on day 1 every 21 days. The concurrent

### Table 1. Selected studies of gemcitabine given concurrently with radiation

<table>
<thead>
<tr>
<th>Primary investigator</th>
<th>Phase</th>
<th>N</th>
<th>Population</th>
<th>Chemotherapy regimen</th>
<th>Radiation regimen</th>
<th>Efficacy</th>
<th>Acute grade 3–4 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalliet, 1998</td>
<td>II</td>
<td>8</td>
<td>Stage IIIa: 50% Stage IIIb: 50%</td>
<td>Gemcitabine 1000 mg/m² weekly × 6 weeks (NOT RECOMMENDED)</td>
<td>2 Gy/day for total of 60 Gy</td>
<td>87.5% response rate</td>
<td>Hematological: 25% Pneumonitis: 75% Oesophagitis: 50% Toxic death: 38%</td>
</tr>
<tr>
<td>Fossella, 2001</td>
<td>I</td>
<td>21</td>
<td>Stage II–III</td>
<td>Gemcitabine 125–190 mg/m² weekly × 7 weeks</td>
<td>1.8 Gy/day for total of 63 Gy</td>
<td>Estimated 55 week median survival</td>
<td>Hematological: not reported Oesophagitis: 30% Pneumonitis: 12% Oesophagitis: 24% Oesophagitis: 18%</td>
</tr>
<tr>
<td>Blackstock, 2001</td>
<td>I</td>
<td>17</td>
<td>Stage IIIa: 82% Stage IIIb: 18%</td>
<td>Gemcitabine 10–50 mg/m² twice weekly × 6 weeks</td>
<td>1.8–2.0 Gy/day for total of 60 Gy</td>
<td>88% response rate and 13 month median survival</td>
<td>Hematological: 53% Pneumonitis: 14% Oesophagitis: 52%</td>
</tr>
<tr>
<td>Vokes, 2002</td>
<td>II</td>
<td>62</td>
<td>Stage IIIa: 63% Stage IIIb: 37%</td>
<td>Gemcitabine 600 mg/m² day 1, 8 plus cisplatin 80 mg/m²/week day 1 every 21 days × 2 cycles</td>
<td>2 Gy/day for total of 66 Gy</td>
<td>74% response rate, 18.3 month median survival</td>
<td>Hematological: 0% Oesophagitis: 0% Pneumonitis: 3% Oesophagitis: 3% All: 30%</td>
</tr>
<tr>
<td>Trodella, 2003</td>
<td>II</td>
<td>39</td>
<td>Stage IIIa/N2</td>
<td>Gemcitabine 350 mg/m² weekly × 5 weeks</td>
<td>1.8 Gy/day or 1.2 Gy BID for total of 50.4 Gy</td>
<td>85% response rate</td>
<td>Hematological: 3% Pneumonitis: 0% Oesophagitis: 0%</td>
</tr>
<tr>
<td>van Putten, 2003</td>
<td>I</td>
<td>27</td>
<td>Stage IIIa: 14 pts Stage IIIb: 13 pts</td>
<td>Gemcitabine 300–450 mg/m² weekly × 6 weeks</td>
<td>2 Gy/day for total of 60 Gy</td>
<td>63% response rate and 61 week median survival</td>
<td>Hematological: 0% Pneumonitis: 3% Oesophagitis: 3%</td>
</tr>
<tr>
<td>Choy, 2005</td>
<td>I</td>
<td>27</td>
<td>Stage IIIa/IIIb</td>
<td>Gemcitabine 450 mg/m² day 1, 8 plus carboplatin AUC=2 day 1, 8 every 21 days × 2 cycles</td>
<td>1.8–2.0 Gy/day for total 63 Gy</td>
<td>Not reported</td>
<td>Hematological: 0% Pneumonitis: 3% Oesophagitis: 3% All: 30%</td>
</tr>
</tbody>
</table>

*This study included a consolidation phase of full dose gemcitabine and cisplatin.
*This study included an induction phase of full dose gemcitabine and cisplatin.
*This study included a consolidation phase of full dose gemcitabine and carboplatin.
phase used gemcitabine 600 mg/m^2 on days 1 and 8 with cisplatin 80 mg/m^2 on day 1 every 21 days for two cycles along with 2 Gy/day of radiation. It is interesting to note that the 600-mg/m^2 concurrent gemcitabine dose was not supported by phase I data. Although the design of the study did not allow for a statistical comparison among the arms, the median survival times for arms 1, 2, and 3 (18.3, 14.8, and 17.7 months, respectively) and response rates (74%, 67%, and 73%, respectively) were clinically similar, with the gemcitabine arm having a numerically higher 3-year survival rate (28% versus 19% for arm 2 and 23% for arm 3). The arm 1 toxicities reported during the concurrent phase revealed higher hematologic and gastrointestinal toxicities compared with studies that used a lower gemcitabine dose. The authors concluded that induction chemotherapy followed by concomitant chemoradiotherapy in patients with unresectable stage III disease was safely administered at the studied schedule and dose. The authors noted that the gemcitabine arm had the most severe toxicity profile in the concurrent phase of the trial; a potential explanation for this would be the use of a higher gemcitabine dose.

**gemcitabine given sequentially after radiation**

If a gemcitabine-based regimen is planned after radiation, initiation of gemcitabine should not begin until the acute effects of radiation therapy are resolved. There have been published results of full-dose gemcitabine (both as a single agent and in combination with a platinum agent) administered following a radiation regimen. The results seen in these studies do not indicate enhanced toxicity with gemcitabine following radiation therapy.

Gemcitabine used as consolidation therapy has been studied in several trials. In this setting, single-agent gemcitabine and gemcitabine in combination with cisplatin, carboplatin, docetaxel, and vinorelbine have been evaluated (Table 2). It is difficult to analyze the toxicities because the primary focus of these trials was either induction or concurrent chemotherapy, and as such, the results for the consolidation phase were not discussed. However, the toxicity profile of gemcitabine in situations where gemcitabine was administered after radiation does not appear to be different than that of radiation-naïve patients, except for instances of radiation recall [15]. Radiation recall events are usually cutaneous or mucosal reactions or pneumonitis in the treatment field of prior radiotherapy that are precipitated by drug treatment; these events have been reported with many cytotoxic drugs, such as doxorubicin, etoposide, paclitaxel, and tamoxifen [16]. The cutaneous reports were primarily skin erythema and pruritus [15–18], while the noncutaneous reactions included hepatic necrosis [19], optic neuritis, brainstem radio necrosis, lymphangitis [18], and abdominal wall tenderness [18, 20]. In general, radiation recall events have been rarely reported with gemcitabine.

**Table 2. Selected studies of gemcitabine given sequentially after radiation**

<table>
<thead>
<tr>
<th>Primary investigator</th>
<th>Phase</th>
<th>N</th>
<th>Population</th>
<th>Consolidation regimen</th>
<th>Efficacy</th>
<th>Acute grade 3–4 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinolas, 2000^a</td>
<td>II</td>
<td>33</td>
<td>Stage IIa: 15% Stage IIb: 85%</td>
<td>Gemcitabine 1000 mg/m^2 day 1, 8, 15 plus either: Carboplatin 400 mg/m^2 day 1 or cisplatin 100 mg/m^2 day 1 every 28 days x 2 cycles</td>
<td>13.8 month median survival, 62% 1-year survival and 19% 2-year survival</td>
<td>Hematological: 70% Pneumonitis: 0% Oesophagitis: 34%</td>
</tr>
<tr>
<td>Fossella, 2001^b</td>
<td>I</td>
<td>21</td>
<td>Stage II–III</td>
<td>Gemcitabine 1000 mg/m^2 day 1, 8, 15 plus cisplatin 60 mg/m^2 day 1 x 4 cycles</td>
<td>Estimated 55 week median survival</td>
<td>Not reported</td>
</tr>
<tr>
<td>Boyd-Sirard, 2002^c</td>
<td>II</td>
<td>16</td>
<td>Stage IIIa: 56% Stage IIb: 44%</td>
<td>Gemcitabine 1000 mg/m^2 6 doses over 56 days</td>
<td>Not reported</td>
<td>Hematological: 69% Other: not reported</td>
</tr>
<tr>
<td>Featherstone, 2002^d</td>
<td>I</td>
<td>11</td>
<td>Stage IIIa: 45% Stage IIb: 55%</td>
<td>Gemcitabine 1200 mg/m^2 day 1, 8 plus vinorelbine 30 mg/m^2 day 1, 8 x 1 cycle</td>
<td>68 weeks median survival</td>
<td>Hematological: not reported Pneumonitis: 27% Oesophagitis: 18% Toxic death: 18%</td>
</tr>
<tr>
<td>Zwitter, 2002^e</td>
<td>I-II</td>
<td>23</td>
<td>Stage IIb</td>
<td>Gemcitabine 1250 mg/m^2 day 1, 8 x 1 cycle or gemcitabine 1250 mg/m^2 day 1, 8 plus cisplatin 70 mg/m^2 day 1 x 1–4 cycles</td>
<td>51% 1-year survival and 43% 2-year survival</td>
<td>Hematological: 17% Pneumonitis: 0% Oesophagitis: 13%</td>
</tr>
<tr>
<td>Garrido, 2005^f</td>
<td>II</td>
<td>31</td>
<td>Stage IIIa: 3% Stage IIb: 97%</td>
<td>Gemcitabine 1200 mg/m^2 day 1, 8 plus docetaxel 40 mg/m^2 day 1, 8 every 21 days x 2 cycles</td>
<td>Not reported</td>
<td>Hematological: 22% Pneumonitis: 4% Oesophagitis: 22%</td>
</tr>
</tbody>
</table>

^aThis study included an induction phase of full-dose paclitaxel and carboplatin, and a concurrent phase of paclitaxel and carboplatin with radiation.

^bThis study included an induction phase of full-dose gemcitabine and cisplatin, and a concurrent phase of single-agent gemcitabine with radiation.

^cThis study included a concurrent phase of single-agent gemcitabine with radiation.

^dThis study included an induction phase or full dose gemcitabine with either cisplatin or carboplatin, and a concurrent phase of vinorelbine with either cisplatin or carboplatin.

^eThis study included a concurrent phase of docetaxel with carboplatin and radiation.

^fThis study included an induction phase of full dose gemcitabine and vinorelbine, and a concurrent phase of gemcitabine and vinorelbine with radiation.
administration; however, if observed, gemcitabine should be discontinued, and a treatment of glucocorticoids or non-steroidal anti-inflammatory agents and supportive therapy including antihistamines should be administered [16, 18]. Complete resolution occurs in about a half of patients, while others require prolonged corticoid treatment.

**gemcitabine given sequentially before radiation**

If a gemcitabine-based regimen is planned prior to radiation, there should be a break of at least 1 week before the start of radiation to minimize the potential for unanticipated radiosensitization. According to preclinical studies, the radiation-enhancing effects of gemcitabine typically last 24 to 72 h. In an emergency situation, it may be necessary to administer radiation therapy immediately following the cessation of gemcitabine; however, there are no data regarding the effects of gemcitabine and palliative radiation therapy to the central nervous system.

Full-dose gemcitabine-based combinations have been studied in the induction setting in several trials. The majority of published data is with gemcitabine and cisplatin [14, 19–22], although there are also published studies of gemcitabine and carboplatin [23–28], vinorelbine [29], and triplet therapy with paclitaxel and a platinum agent [30–32]. Most studies used two to three cycles of induction. The CALGB study 9431 initiated concurrent radiotherapy 2 weeks following induction therapy [14].

In randomized studies, the combination of gemcitabine and cisplatin has been compared with another cisplatin-based combination, either with etoposide, vinorelbine, or paclitaxel [14, 19–22]. The gemcitabine dose used in most of these studies was 1250 mg/m² on days 1 and 8, while the cisplatin dose ranged from 50 to 100 mg/m² on day 1 every 21 days. Of note, one non-randomized study began with cisplatin 100 mg/m² and was later amended to 70 mg/m² due to cisplatin-related nonhematologic toxicities [22]. In all of the randomized studies, the response rates of gemcitabine and cisplatin after induction were numerically similar to that of the comparator arms. The response rates ranged from 40 to 60%. The toxicities seen with the gemcitabine with cisplatin induction regimen were similar to those seen when the combination was given without radiation in metastatic NSCLC. The primary toxicities were neutropenia, thrombocytopenia, anemia, nausea, and vomiting.

In studies evaluating the combination of gemcitabine and carboplatin administered before radiation therapy [23–28], the gemcitabine doses have ranged from 1000 to 1250 mg/m² on days 1 and 8 with the carboplatin dose ranging from AUC of 5.0 to 5.2 on day 1 every 21 days. Response rates ranged from 30% to 65%, which were similar to those in the gemcitabine with cisplatin studies. The toxicities seen were also similar to the toxicities associated with gemcitabine and cisplatin, except that more thrombocytopenia and less nausea and vomiting were reported with the gemcitabine and carboplatin combination.

**futures directions for gemcitabine and radiation in NSCLC**

The treatment of stage III NSCLC is advancing. The results of key studies are reshaping how to administer radiation and chemotherapy. These studies have focused on how radiation and chemotherapy can be most effectively combined.

The goal of the Locally Advanced Multimodality Protocol (LAMP) trial [30] was to determine the optimal order that radiation and chemotherapy should be given in patients with unresected stage III NSCLC. There were three arms of the study that included chemotherapy followed by radiation, chemotherapy followed by radiation concurrent with chemotherapy, and radiation concurrent with chemotherapy followed by chemotherapy. The chemotherapy used in this trial was paclitaxel and carboplatin, while the dose of radiation was 63 Gy. The arm of radiation concurrent with chemotherapy followed by chemotherapy showed the longest median survival time along with the most grade 3 esophagitis and overall lung toxicities. The authors concluded that this arm should serve as the core for future trials.

RTOG 9410 [31] was planned to compare induction chemotherapy with concurrent chemotherapy in patients with stage II and III NSCLC. There were three arms of the study, which included chemotherapy followed by radiation, chemotherapy concurrent with standard radiation, and chemotherapy concurrent with hyperfractionated radiation. The chemotherapy used in this trial was cisplatin and vinblastine, except for the hyperfractionated arm, which used cisplatin and etoposide. The hyperfractionated arm improved local control, but it did not improve survival. The chemotherapy with standard radiation arm produced a statistically significant longer median survival than the sequential arm. The sequential arm had higher rates of grade 3 and 4 nonhematologic toxicities, although late toxicity rates were similar across all arms.

Southwest Oncology Group (SWOG) study 9504 [32] was a single-arm study that evaluated consolidation therapy following concurrent chemoradiation in patients with stage IIIb NSCLC. The concurrent regimen was cisplatin and etoposide given with 61 Gy of radiation; the consolidation therapy was a standard docetaxel regimen. The median survival was 26 months. Grade 4 neutropenia was seen in more than half the patients during consolidation docetaxel. Even though the results need to be substantiated in a phase III setting, this trial is encouraging because the survival endpoints are some of the highest historically seen in stage IIb NSCLC patients.

On the basis of these results and those of other studies, the standard use of chemotherapy and radiation is evolving into concurrent usage with or without consolidation chemotherapy. Gemcitabine was not included in any of the studies referred to above; however, as reviewed in this article, gemcitabine has been used in similar trial settings.

The initial study of gemcitabine and radiation produced unacceptable results. Lessons were learned from this study, and future studies demonstrated that in a clinical trial setting, gemcitabine and radiation can be given safely, and lead to high response rates. Because of the radiation-enhancing effects of...
gemcitabine and the severe toxicity seen in this initial trial, caution needs to be used when combining these modalities.

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references