A Phase I Study of Gemcitabine with Concurrent Radiotherapy in Stage III, Locally Advanced Non-Small Cell Lung Cancer

John W. G. van Putten, Allen Price, Annya H. D. van der Leest, Anne Gregor, Felicity A. Little, and Harry J. M. Groen

Departments of Pulmonary Diseases [J. W. G. v. P., H. J. M. G.], and Radiotherapy [A. H. d. v. d. L.], University Hospital, Groningen, 9700 RB the Netherlands, and Department of Oncology, Western General Hospital, Edinburgh, United Kingdom [A. P., A. G., F. A. L.]

ABSTRACT

Purpose: Our goal was to find the maximum tolerated dose of gemcitabine administered concurrently with thoracic radiotherapy in locally advanced non-small cell lung cancer (NSCLC).

Patients and Methods: Patients with stage III NSCLC and a radiation planning volume less than 2000 cm³ were included. Treatment consisted of 6 weeks of thoracic radiation, 2 Gy daily for 5 days a week for a total dose of 60 Gy. Planning with multiple field arrangements and three-dimensional conformal technique was used. Patients were treated with gemcitabine, starting with a dose of 300 mg/m² in the 1st week of radiation. In subsequent cohorts, the weekly dosing frequency of gemcitabine was increased until weekly administration was reached. Thereafter, the doses of weekly gemcitabine were increased. Toxicity was measured using Common Toxicity of the National Cancer Institute (CTC), acute Radiation Therapy Oncology Group (RTOG), and late RTOG/European Organization for Research and Treatment of Cancer (EORTC) rating scales.

Results: Twenty-seven patients were included, of whom 14 had stage IIIa and 13 had stage IIIb. Dose-limiting toxicity was grade 3 esophagitis and grade 3 radiation pneumonitis in the patient cohort receiving gemcitabine 450 mg/m² once weekly. The mean actual treated radiation volume was 760 cm³ (range, 289-1718 cm³).

Conclusions: The maximum tolerated dose and frequency of gemcitabine in locally advanced NSCLC is 300 mg/m² once weekly during 6 weeks of thoracic radiotherapy, as long as the treatment volume does not exceed 2000 cm³.

INTRODUCTION

One-third of patients with NSCLC² present with locally advanced disease with the tumor irresectable because of either locoregional invasion or metastases to mediastinal lymph nodes. Treatment of choice for this stage III NSCLC will usually include radiotherapy, when it is technically possible to include the entire tumor and its metastases within a safe radiation volume (1). Most patients will die from distant metastases, but locoregional progression also occurs in a significant number of patients. Survival outcome is poor with a median survival of 13 months and a 5-year survival between 5 and 9% (2). When tumor evaluation is performed with imaging techniques only, thoracic radiotherapy achieves initial local control in about 50% of patients, but when endobronchial biopsies are included, malignancy is still present in 85% of patients (3).

With an increasing number of long-term survivors, the role of adding chest radiation after chemotherapy has been proven (4). In a meta-analysis, the sequential combination of chemotherapy and radiotherapy showed a small, but significant, advantage in 5-year survival (5). Recently, it has been suggested that concurrent administration of chemotherapy and radiotherapy should be the standard for stage III NSCLC (6, 7). The simultaneous administration of chemotherapy and radiotherapy has the advantage of systemic tumor cell killing and radiosensitization by the chemotherapy. Daily cisplatin has been used concurrently with suboptimal radiation schedules, which has given rise to various results (8-10). Moreover, the addition of weekly or continuous carboplatin during 6 weeks of irradiation did not show consistent changes in local tumor control and survival (11, 12, 13) but the addition of daily carboplatin/etoposide to thoracic radiotherapy did improve local control and survival (14). Taken together, these data suggest a benefit from concomitant chemoradiotherapy, but there is a need for additional data regarding the optimal timing and sequence of chemotherapy and radiotherapy in these patients.

Gemcitabine is an active chemotherapeutic agent in NSCLC and induces tumor responses in about 22% of patients with stage IV disease (15, 16). It has also been observed to have potent radiosensitizing properties in vivo and in vitro (17, 18). In vitro studies reveal that gemcitabine induces its radiosensitizing effect in the cell within 2 h, and this effect remains for about 72 h (19). Therefore, administration of gemcitabine once a week, at least 2 h before radiation, appears to be a reasonable scheduling for radiosensitization.

2 The abbreviations used are: NSCLC, non-small cell lung cancer; CTC, Common Toxicity of the National Cancer Institute; RTOG, Radiation Therapy Oncology Group (toxicity); MTD, maximum tolerated dose; PEV1, forced expiratory volume in 1 s; CT, computed tomography; PTV, planning treatment volume; DLT, dose-limiting toxicity; DLco, diffusion of carbon monoxide.
In this Phase I study, the radiosensitizing property of gemcitabine on a daily radiation dose was studied in stage III NSCLC. The primary objective of our study was to determine the MTD for a weekly schedule of gemcitabine combined with radical thoracic radiotherapy for patients with irresectable stage III NSCLC.

PATIENTS AND METHODS

The Medical Ethical Committees of both university hospitals approved the multicenter trial. All of the patients gave written informed consent before they were enrolled in the study.

Eligibility Criteria. Patients were considered eligible when they met all of the following criteria: (a) histological or cytological proof of NSCLC; (b) pathologically proven stage IIIa or IIIb not amenable for surgical resection; (c) no prior chemo- or radiotherapy; (d) Eastern Cooperative Oncology Group performance status 0–2; (e) hemoglobin ≥9.1 g/liter (5.6 mmol/liter); (f) white blood count ≥3.0 × 10^9/liter; (g) platelets ≥100 × 10^9/liter; (h) adequate pulmonary function, defined as FEV1 ≥1.5 L or FEV1 between 1.0 and 1.5 liters if DLco was ≥50% of the amount predicted; (i) adequate renal function (serum creatinine below 135 μmol/liter); (j) liver function (serum bilirubin <1.5 times the upper normal limit and/or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) less than three times the upper normal limit); and (k) measurable disease on CT scan. Exclusion criteria included: (a) uncontrolled infection; (b) hypercalcemia; (c) superior vena cava syndrome; and (d) a PTV >2000 cm^3 according to the guidelines of the International Commission on Radiation Units and Measurements (20).

Radiotherapy. The overall dose of radiation was 60 Gy administered over 6 weeks with daily fractions of 2 Gy administered for 5 days each week. Planning CT scan was performed in the supine position. The PTV encompassed the radiological visible primary tumor (GTV) with a margin of radiological normal and uninvolved tissue of 1.5 cm in the transverse and 2 cm in the longitudinal margins. Mediastinal lymph nodes >1.5 cm in smallest diameter on CT were considered to be involved and were included in the clinical target volume (CTV) with a margin of 1 cm in transverse and 1.5 cm in longitudinal direction. The elective nodal irradiation field included only one adjacent station of unenlarged lymph nodes on CT scan. For N1 tumors, the ipsilateral hilum was included; for N2 tumors, the ipsilateral mediastinal nodes in position 10, 7, and 4 according to Naruke’s classification system, were included; and for N3 tumors, one additional uninvolved lymph node station was included. The margin of normal tissue for these regional lymph nodes was 1 cm in transverse and 1.5 cm in longitudinal direction. The PTV was defined as the clinical target volume with the aforementioned elective margins and elective lymph node stations and was not allowed to exceed 2000 cm^3. As prophylactic irradiation was administered to only one lymph node station the maximal volume of 2000 cm^3 is rather large and includes a typical and representative population of patients with stage III NSCLC, who are normally considered for high-dose radiotherapy. Using multiple-field arrangement with the use of three-dimensional conformal technique, we irradiated the PTV. Irradiation was administered with megavoltage photons of at least 6 MeV. The dose of 60 Gy was specified at the isocenter of the central axis and was corrected for pulmonary heterogeneity. The spinal cord was not allowed to receive more than 80% of the tumor dose, and the maximum length of the esophagus in PTV would not exceed 15 cm at any point. The heart should not receive the total dose to more than 30% of its volume and would not receive more than 50% of the total dose to 50% of its volume. In case of RTOG grade 4 esophagitis, radiation was stopped.

Gemcitabine. Gemcitabine (Eli Lilly, Indianapolis, IN) was administered as a 30-min i.v. infusion on the 1st day of the week at least 2 h before irradiation. Patients were entered in cohorts of three, and dose escalation was allowed as the acute toxicity profile had been assessed. In the first cohort, 300 mg/m^2 gemcitabine was administered on the 1st day of 6 weeks radiotherapy (Table 1). In the second cohort, the same dose was administered on days 1 and 15, and in the third cohort, on days 1, 15 and 29. From the third cohort, inclusion of patients was held for 3 months after the completion of irradiation in the last patient, to enable the scoring of toxicity before dose-escalation for the next cohort was allowed. From the fourth cohort, the weekly dosing frequency of gemcitabine was further increased (Table 1). Thereafter, the doses of weekly gemcitabine would be increased to 450 mg/m^2 in the seventh cohort and to 600 mg/m^2 in the eighth cohort. At the MTD level, a total of nine patients would be treated. The dose of gemcitabine was reduced to 50% in case of granulocytes between 0.5 and 1.0 × 10^9/liter or platelets between 50 and 75 × 10^9/liter or CTC grade 3 non-hematological toxicity, and was omitted in case of granulocytes below 0.5 × 10^9/liter, platelets below 50 × 10^9/liter, RTOG grade 3 esophagitis or pneumonitis, or CTC grade 4 non-hematological toxicity. Antiemetics ondansetron 8 mg or domperidone 10 mg was administered p.o. 4 h before each gemcitabine infusion.

MTD. The MTD was defined as the highest dose of gemcitabine that could be safely administered to a patient in combination with radiotherapy, producing tolerable, manageable, and reversible toxicity. The assessment of MTD was based on acute as well as late toxicity of the combination treatment. MTD was reached at the highest dose level of gemcitabine at which DLT did not occur in more than 2 of 6 or 3 of 9 patients. DLT was defined as absolute granulocytes <0.5 × 10^9/liter for more than 7 days; CTC grade 4 thrombocytopenia; CTC grade 3 or 4 nonhematological toxicity (excluding alopecia, nausea, and vomiting); acute RTOG grade 3 or 4 with respect to lung.

Table 1 Dose and dosing frequency of gemcitabine in subsequent cohorts of patients during 6 weeks of radiotherapy

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose (mg/m^2)</th>
<th>Days administered</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>300</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
<td>1, 15</td>
</tr>
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<td>3</td>
<td>300</td>
<td>1, 15, 29</td>
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<tr>
<td>4</td>
<td>300</td>
<td>1, 8, 15, 29</td>
</tr>
<tr>
<td>5</td>
<td>300</td>
<td>1, 8, 15, 22, 29</td>
</tr>
<tr>
<td>6</td>
<td>300</td>
<td>1, 8, 15, 22, 29, 36</td>
</tr>
<tr>
<td>7</td>
<td>450</td>
<td>1, 8, 15, 22, 29, 36</td>
</tr>
<tr>
<td>8</td>
<td>600</td>
<td>1, 8, 15, 22, 29, 36</td>
</tr>
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upper gastrointestinal, or esophagus; or late RTOG grade 3 or 4 with respect to lung, heart, esophagus, and spinal cord.

Evaluation and Response Assessment. Before treatment, patients were assessed with medical history and physical examination including Eastern Cooperative Oncology Group performance status, complete blood cell count, liver function tests and serum creatinine, CT of the chest and upper abdomen, bone scan, electrocardiogram, and pulmonary function tests. Pulmonary function tests included total lung capacity, forced vital capacity, FEV1, and DLco. During radiotherapy, a toxicity evaluation and a complete blood cell count were performed weekly. One month after the end of radiotherapy, toxicity was assessed and pretreatment tests were repeated. Tumor response was evaluated by CT of the chest, according to standard WHO criteria (21). Thereafter, patients were scored for toxicity and evaluated for tumor progression and pulmonary function every 3 months. Acute toxicity from the start to 3 months after the end of radiotherapy was scored using CTC and RTOG acute radiation morbidity scoring criteria. Late toxicity more than 3 months after the end of radiotherapy was scored using CTC and RTOG acute radiation morbidity scoring criteria. Late toxicity more than 3 months after the end of radiotherapy was scored according to the late RTOG scoring criteria.

Statistics. Descriptive statistics were performed for toxicity. Time to progression and survival were measured from the date of initiation of therapy, using the Kaplan-Meier product-limit method. Data of pulmonary function tests before and after treatment were analyzed using ANOVA in a repeated measurement design. Pearson’s product-limit coefficient of correlation was calculated for PTV and changes in pulmonary function tests. Values of \( P < 0.05 \) were considered statistically significant.

RESULTS

Patient Characteristics. From January 1997 until March 2000, a total of 27 patients were included in this study. This lengthy period of accrual was caused by the interval between each dose level to exclude late toxicities. All of the patients were assessable for toxicity and response. Table 2 lists the characteristics of all of the patients. Their median age was 61 years (range, 43–77 years); all of the patients had a good ECOG performance status. Fourteen patients were staged as IIIa, and 13 had stage IIIb. Median PTV was 760 cm\(^3\) (range, 289–1718 cm\(^3\)). All of the patients completed study protocol treatment.

Toxicity. Hematological toxicity was not observed, except for temporary lymphocytopenia in 89% of patients attributable to the radiotherapy. Dose reductions or omissions of gemcitabine because of hematological toxicity were not necessary.

In all cohorts, grade 2 nonhematological toxicity was observed (Tables 3 and 4). Initially, three patients were treated in each cohort until in the seventh cohort (weekly gemcitabine, 450 mg/m\(^2\)) when DLT was observed in two of three patients. The DLT was acute RTOG grade 3 esophagitis during the 5th week of radiotherapy and acute RTOG grade 3 pneumonia in the 1st week after the end of radiotherapy. In the patient with grade 3 esophagitis, the last two doses of gemcitabine were omitted, and dysphagia gradually decreased over 2 months. In the patient with grade 3 radiation-induced pneumonitis, dyspnea rapidly resolved after the start of steroids without permanent impairment of pulmonary function. At MTD level of gemcitabine 300 mg/m\(^2\), six additional patients were included. Toxicity at this level was acceptable, although grade 3 toxicity (not defined as DLT) was observed in two of nine patients, one with acute RTOG grade 3 upper gastrointestinal toxicity (anorexia with weight loss) and the other with short-lasting CTC grade 3 vomiting after the end of radiotherapy without accompanying esophagitis. Nonhematological toxicity observed in all of the cohorts was mainly dysphagia and esophagitis. Scoring of late toxicity during 1-year follow-up has been completed in 25 patients, and only grade 1 and 2 late RTOG toxicities were observed (Table 4). All of the reported events during protocol treatment (Table 5) were not dose related.
Table 5  Summary of all of the reported events during Phase I study of radiotherapy combined with gemcitabine

<table>
<thead>
<tr>
<th>Event</th>
<th>No. (%) of patients with event (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patients with ≥1 event</td>
<td>27 (100)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (48.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>11 (40.7)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>Cough increased</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>Fever</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (11.1)</td>
</tr>
</tbody>
</table>

The majority of gemcitabine doses (95%; 112 of 117 planned doses) were administered as assigned. In cohort 6 and 7, one patient omitted two doses on days 29 and 36 because of esophagitis. In the sixth cohort, one patient had an omission on day 15 because of an intercurrent bronchitis. All of the patients received radiotherapy to a total dose of 60 Gy as was designed. The median duration of irradiation was 5.6 (range, 5.6 to 6.7) weeks. Eight patients received more than the maximum allowable dose of radiation to parts of the ipsilateral or contralateral lung. In two patients, the heart or spinal cord also received a higher dose than allowed. Adverse events associated with the increased exposure to irradiation were not observed.

Pulmonary infiltrates and fibrosis outside the radiation field were not observed. The total lung capacity, forced vital capacity, and FEV1 did not change significantly after treatment, but Dlco showed a slight, but significant, decrease after radiation (P = 0.04). This decrease in Dlco was not correlated to the PTV or gemcitabine dose.

Tumor Response. Among 27 patients, 4 complete responses (in 1 patient proven by surgical resection) and 13 partial responses were confirmed, and 9 patients had stable disease after treatment. One patient had progressive disease outside the radiation volume shortly after the end of radiation. Tumor response rate was 63% (95% CI, 42–80%). Median time to progression was 39 weeks (95% CI, 23–55 weeks), and 13 patients had developed progressive disease. The first site of progression was seen within the target volume in seven patients, and at distant sites in six patients. Median survival time was 61 weeks (95% CI, 38–81 weeks), with a 1-year survival of 81% and 2-year survival of 41%. After progression occurred, four patients received additional chemotherapy until the moment of analysis.

DISCUSSION

Induction chemotherapy has been shown to improve survival in patients with stage III NSCLC, but it is unclear to what extent this reflects the control of undiagnosed metastatic disease or an improved effectiveness of local treatment by the reduction of tumor volume. Because survival in stage III NSCLC is related to local tumor response and control, improvement may be achieved by intensification of local therapy. Potentiation of radiation may be achieved by higher radiation doses or by hyperfractionation to reduce overall treatment time. Selective sensitization of the cancer cells by a radiosensitizer is theoretically another attractive way of achieving an increased local effect of radiotherapy. However, these approaches will also increase radiation-related toxicity, especially pneumonitis and esophagitis, which will limit the extent to which local antitumor effects can be increased.

Gemcitabine appears to be a strong radiosensitizer at doses substantially less than those required for cytotoxic effects (22). Major tumor responses were observed in a feasibility study with gemcitabine 1000 mg/m² each week during 6 weeks radiotherapy, but with unacceptable toxicity, mainly radiation pneumonitis related to the large irradiated volumes (23, 24). Therefore, the present study was carried out using strict radiotherapy criteria with three-dimensional conformal technique, only one station of elective nodal irradiation, a PTV not exceeding 2000 cm³, and cautious dose escalation of gemcitabine to minimize radiation-induced complications. At the recommended dose level, radiation pneumonitis was not observed, and esophagitis was seen in one of nine patients. Radiation-induced pulmonary infiltrates and fibrosis were not observed outside the irradiated fields. Significant changes in lung volumes were not observed. The slight decrease in diffusion capacity is not clinically relevant and is probably related to radiation-induced damage to the pulmonary vasculature. However, the actual PTV irradiated was small because we omitted elective nodal irradiation, and this is likely to be important in limiting toxicity. This will be relevant to future studies because toxicity is related to the volume of irradiated (normal) tissue (25). On the other hand, more accurate staging in NSCLC, especially with fluorodeoxyglucose positron emission tomography, gives us the opportunity for better selection and definition of the optimal treatment and radiation field (26, 27).

Recently, several studies have investigated the combination of gemcitabine with thoracic radiotherapy. An Italian group has reported a MTD of 350 mg/m² gemcitabine once weekly in combination with a subtherapeutic radiation dose of 50 Gy, but the details of the radiation volumes were not given (28). A study of weekly gemcitabine in which larger volumes were used with a radiotherapy dose of 63 Gy, followed by adjuvant cisplatin-gemcitabine, reported a MTD of gemcitabine at 190 mg/m² (29). Another group found a MTD for gemcitabine at only 70 mg/m²/week when administered as twice weekly doses in combination with 60 Gy thoracic irradiation (30). Whether gemcitabine at these low doses has systemic cytotoxic effects is not known but seems unlikely.

Other cytotoxic agents have been investigated for their radiosensitizing effect in locally advanced NSCLC, including paclitaxel (31), docetaxel (32), and irinotecan (33). The observed DLT with these drugs was also mainly reversible esophagitis. Until now, none of these agents has been studied in a randomized Phase III study to establish its role as a radiosensitizer in NSCLC.
The exact mechanism of radiosensitization induced by gemcitabine is unknown. Induction of double-strand breaks in DNA is considered to be one of the most important cytotoxic effects of radiotherapy. Several possible mechanisms for the radiosensitizing effects of gemcitabine have been discovered, including changes in nucleotide pools and cell cycle distribution. In vitro, gemcitabine seems to impair homologous recombination, which suggests that radiation-induced DNA damage cannot be properly repaired and results in increased tumor cell killing (34).

In this Phase I trial, we found in a representative group of stage III NSCLC patients that gemcitabine 300 mg/m² each week is the MTD in combination with 60 Gy thoracic radiotherapy. With the exception of contradictory data on cisplatin and carboplatin, the role of radiosensitizers in NSCLC has not been evaluated in randomized studies. Because gemcitabine is one of the strongest radiosensitizers known in NSCLC, the clinical usefulness of this combined approach should be further evaluated. On the other hand we consider the combination with systemic treatment (e.g., induction chemotherapy) necessary to further improve the efficacy of this approach. The Cancer and Leukemia Group B has already initiated a study with induction chemotherapy and a higher dose of concomitant gemcitabine of 600 mg/m² (35).

Therefore, our single-agent concurrent chemoradiotherapy regimen may probably be attractive for older patients or patients with comorbidity who are not candidates for systemic chemotherapy.

REFERENCES


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