Phase II study of weekly gemcitabine in advanced non-small cell lung cancer

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New active agents are needed to develop effective systemic therapy against Stage IIIB-IV non-small cell lung cancer (NSCLC). The aim of the present study was to assess the efficacy and toxicity of gemcitabine, a novel nucleoside analogue with significant preclinical activity, as a single-agent therapy.

Forty-three patients with previously untreated Stage IIIB-IV NSCLC were included. Gemcitabine was administered intravenously over 30 min on Days 1, 8, and 15 of each 28-day cycle at a dose of 1250 mg m$^{-2}$.

Thirty-seven patients were evaluable for response. There were seven partial responses giving an overall response rate of 19% (95% confidence interval 8-35%). Median duration of response was 6 months. One-year survival and median survival for all patients were 33% and 8 months, respectively. Toxicity of the treatment was mild. World Health Organization (WHO) Grade 3-4 leukopenia was detected in 11% of the patients. Mild (WHO Grade 1-2) nausea was the most frequent subjective side-effect with a rate of 82%. Mild rash and peripheral oedema were typical side-effects of gemcitabine with rates of 19 and 9%, respectively.

In conclusion, single-agent gemcitabine is an active and well-tolerated treatment for Stage IIIB-IV NSCLC patients.

Introduction

It is estimated that more than 80% of patients with non-small cell lung cancer (NSCLC) have metastases at the time of diagnosis, and systemic therapy is therefore the only curative potential (1). Without treatment, the median survival of these patients has been reported to be from 4.5 to 7.5 months (2). In recent meta-analyses, cisplatin-based polychemotherapy has been shown to significantly increase the survival of patients with both locally advanced and metastatic disease (3,4). However, this increase in median survival was only 1.5 months when compared with best supportive care (4). In the meta-analysis by Souquet et al., patients responding to therapy also had an improvement in quality of life (3). This can be explained by the disappearance of tumour-related symptoms. However, the side-effects of combination chemotherapy using cisplatin are well known and, therefore, new, better tolerated and more effective agents are required to improve results in the treatment of Stage IIIB-IV NSCLC.

Gemcitabine is a novel anticancer agent. It is an analogue of deoxycytidine, and resembles cytarabine structurally. Unlike cytarabine, gemcitabine has activity against solid tumours such as ovarian cancer, bladder cancer, breast cancer, and head and neck cancer. Lilenbaum and Green reviewed several Phase II trials of gemcitabine in the treatment of NSCLC that had been reported in abstract form (5). They presented 211 patients with 44 responders (20.9%). Single-agent activity of gemcitabine exceeding 20% has also been documented in further studies (6). The present study was conducted to assess the activity and side-effects of gemcitabine in patients with previously untreated Stage IIIB-IV NSCLC.
Patients and Methods

Between February 1992 and January 1995, 43 patients (32 males and 11 females) with Stage III-B-IV histologically or cytologically confirmed NSCLC entered the study. Patient characteristics are given in Table 1. Entry criteria included: performance status of World Health Organization (WHO) Grade 0–2, age above 18 years, estimated life expectancy of at least 12 weeks, measurable or evaluable disease, no prior chemotherapy, no radiotherapy if the lesion for tumour measurements was located in the irradiated area, adequate bone marrow reserve (haemoglobin ≥100 g l⁻¹, white blood cell count (WBC count) >3.0 x 10⁹ l⁻¹, platelets >100 x 10⁹ l⁻¹), and adequate liver and renal function. Patients with symptoms of severe pulmonary disease, active cardiac disease or significant neurologic disorders, such as central nervous system metastases, as well as patients with uncontrolled hypercalcaemia, were excluded. All patients gave their written consent before starting the treatment. The study was approved by the Ethics Committee of the Division of Pulmonary Medicine and Clinical Physiology, Department of Medicine at the Helsinki University Central Hospital, Finland.

Gemcitabine 1250 mg was administered intravenously over 30 min on Days 1, 8 and 15 of each 28-day cycle. A cycle was thus defined as three consecutive weeks of treatment followed by a week of rest. The protocol allowed a maximum of six cycles. In case of no toxicities after the first cycle, a 20% dose escalation was allowed for the first nine patients in the study. Dose modifications were made according to haematologic parameters. The dose was reduced to 75% if WBC count was 1.0–1.9 x 10⁹ l⁻¹ and/or platelet count 50–99 x 10⁹ l⁻¹, and omitted if WBC count <1.0 x 10⁹ l⁻¹ and/or platelet count <50 x 10⁹ l⁻¹. A treatment which had to be postponed for 3 weeks because of toxicity was discontinued. A minimum of two cycles of gemcitabine were required for response evaluation, which was assessed according to Union Internationale Centre le Cancer (UICC) response criteria (7). Toxicity was evaluated using WHO criteria. Chi-squared test was used for analysis of statistical differences among responders.

Results

One to six cycles (mean 3.2) of gemcitabine were given to each patient. Nine (7%) cycles were given at 120% escalated doses. Seven out of 137 (5%) cycles were given at 75% reduced doses. Leukopenia was the main reason for dose reductions in all cases. Twenty patients received other treatments after discontinuation of gemcitabine. Six of them received radiotherapy alone, 13 patients received another chemotherapy regimen and one patient received both radio- and chemotherapy after gemcitabine.

Response to Treatment

Thirty-seven patients were evaluable for response. There were no complete responses. Seven patients reached partial response (PR) which makes an objective response rate of 19% [95% confidence interval (CI) 8–35%]. In four patients, responses were detected using chest X-ray after two cycles of gemcitabine, and confirmed by computerized tomography (CT) after three to four cycles, i.e. when CT was performed for the first time after starting gemcitabine. In the other three patients, PR was registered after four cycles. Median duration of response was 6 months with a range of 2–8 months. Five of the seven responders were men. The tumour histology of the responders included: three adenocarcinomas, three squamous cell carcinomas and one large cell carcinoma. (Table 2). There were no statistically significant differences between responders in terms of sex or tumour histology. Two of the responders had Stage III-B disease while the others had Stage IV. Partial response in the five patients with Stage IV disease was seen in primary tumours as well as in the metastases. Both patients with the best performance status (WHO Grade 0) had no change (NC) at tumour evaluation. Six of the responders had WHO Grade 1 and one had WHO Grade 2.
TABLE 2. Response by tumour histology, clinical stage and performance status

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<th>Total</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
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<tr>
<td><strong>Histology</strong></td>
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<tr>
<td>Adeno</td>
<td>23</td>
<td>3</td>
<td>14</td>
<td>6</td>
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<tr>
<td>Squamous</td>
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<td>1</td>
<td>1</td>
<td>2</td>
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<td>5</td>
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PR, partial response; NC, no change; PD, progressive disease.

Six patients (all with Stage IV disease) were not evaluable for response due to early death (one patient), patient decision to discontinue at the end of first cycle (three patients) and protocol violation (two patients). The patients who decided to give up the treatment had experienced several side-effects including WHO Grade 2 anaemia, WHO Grade 2 drug-related fever and deep venous thrombosis. One case of protocol violation was the result of gemcitabine treatment being postponed too many times before the second cycle. Protocol violation also occurred in a patient who had received prior chemotherapy and radiotherapy.

PATIENT SURVIVAL

All patients, including the patients who received other treatments after discontinuation of gemcitabine, were evaluated in the survival analysis. Median survival for all patients and by response (PR/NC/PD) were 8 and 18/10/5 months, respectively. One-year survival was 33% for all patients and 71/41/15% for PR/NC/PD, respectively. Median survival by clinical stage (Stages III and IV) and performance status (WHO Grades 0–2) were 18+ and 8 months, and 11, 9 and 4 months, respectively. In fact, five patients are still alive.

TOXICITY

All patients were evaluable for toxicity. Nine patients (21%) were totally free from haematological toxicity. World Health Organization Grade 2 leukopaenia was the most common finding, occurring in 33% of patients, whereas 11% experienced Grade 3-4 leukopaenia. Anaemia was the second most common sign of haematological toxicity, and Grade 1 and 2 anaemia were equally common, each occurring in 21% of patients. World Health Organization Grade 1 thrombocytopenia was detected in 12% of all patients, and the rate of Grade 2 thrombocytopenia was 5%.

Seven patients (16%) suffered no non-haematological toxicity. The most common subjective side-effect was nausea, which was usually mild. World Health Organization Grade 1 and 2 nausea rates were 70 and 12%, respectively, and were manageable with standard anti-emetics. World Health Organization Grade 1 and 2 fever rates were both 21%. Rash (WHO Grade 1) was reported in 19% of the patients, and peripheral oedema in the limbs was experienced by 9% of the patients. No severe renal toxicity, gastrointestinal toxicity or neurotoxicity was observed. There were no deaths directly related to gemcitabine.

Discussion

The objective response rate achieved in this study, i.e. 19% (95% CI 8–35%), is similar to previous reports. Anderson et al. reported a response rate of 20% (95% CI 12–31%) in 82 patients with NSCLC (8). Fifty-four patients received 800 mg m−2 week−1 and 28 patients received 1000 mg m−2 week−1 for 3 weeks followed by a week of rest. The most common toxicities were WHO Grade 3 nausea in 38%, severe neutropaenia (WHO Grade 3–4) in 22% of the patients and peripheral oedema in 40% of the patients. In the latest report by the same group (9), the response rate remained the same although the patient population was expanded to 332 evaluable patients with advanced, inoperable NSCLC. Thirteen percent of the patients had Stage IIIA disease. The dose of gemcitabine used was 800–1250 mg m−2. Abratt et al. reported an objective response rate of 20% which included two complete responses in 84 patients with Stage IIIB-IV NSCLC (10). The patients received gemcitabine at doses of 1000–1250 mg m−2. In an international multicentre study of 161 inoperable Stage III-IV NSCLC patients using higher doses (i.e. 1250 mg m−2), the response rate was 22% (11), but only three achieved complete response. All this suggests that escalating the starting dose from 800 to 1250 mg m−2 does not increase response rate.

Median survival for all patients in the present study was 8 months and the 1-yr survival rate was 33%. These numbers are comparable with the reports by Anderson and Abratt (9,10). However, nearly half of the present study patients received other treatments after gemcitabine which, of course, may affect the
survival. After comparing the patient characteristics of the responders with non-responders, no factor could be found to favour better tumour response or survival.

The toxicity analysis based on 137 chemotherapy cycles showed treatment to be well tolerated. Haematological toxicity was mild. Severe, i.e. WHO Grade 3–4, toxicity was only detected in leukocyte counts (11%). In the Anderson study, WHO Grade 3–4 leukopenia was detected in 7%, WHO Grade 3 4 anaemia was detected in 5%, and WHO Grade 3 4 thrombocytopenia was detected in 2% of the patients evaluable for toxicity (8). Abratt et al. reported even lower haematological toxicity i.e. WHO Grade 3–4 leukopenia in 1% and WHO Grade 3 4 thrombocytopenia in 0-2% of the patients (10), even though the dose of gemcitabine was higher than in the study by Anderson et al.

Non-haematological toxicity was also mild in the present study. Sixteen percent of the patients were totally free from subjective side-effects. The most common side-effect was nausea, which was less severe (WHO Grade 1–2) but slightly more frequent (82%) in the present study patients when compared with Anderson’s (WHO Grade 1–3, 78%) and Abratt’s (WHO Grade 1–3, 68%) studies (8,10).

Peripheral oedema and rash seem to be typical side-effects of gemcitabine. In the present study, these symptoms were mild (WHO Grade 1) and not as common as in previous reports. Peripheral oedema was found in 9% of the present study patients as compared with 40% in Anderson’s and 42% in Abratt’s studies. Rash was detected in only 19% of the present study patients but it was reported in 39 and 44% of Anderson’s and Abratt’s studies, respectively (8,10).

Early responses were achieved frequently by using high doses (1250 mg m⁻²) of gemcitabine: in four cases after two cycles of gemcitabine, and in three cases after four cycles. There were no responses after further cycles, which implies that continuing treatment beyond four cycles in non-responders is not indicated. No unexpected toxicity was observed in the present study patients, while some known, frequent side-effects, e.g. peripheral oedema and rash, were uncommon. Mild toxicity could provide an opportunity to escalate the starting dose, up to 2000 mg m⁻², and further studies are required to assess the optimal dose of gemcitabine.

It is concluded that gemcitabine is active as a single agent against Stage IIIIB-IV NSCLC, but due to the lack of complete responses and the limited duration of responses, gemcitabine should be used in combination with other drugs. The low toxicity of gemcitabine encourages further studies of combinations with other active agents, which could be taxanes or camptothecine analogues.

Acknowledgement

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References