PHASE II TRIAL OF COMBINED RADIOTHERAPY AND DAILY LOW-DOSE CISPLATIN FOR INOPERABLE, LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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With the use of cis-diamminedichloroplatinum(II), cisplatin, to enhance the effect of radiation a combined modality approach was designed to treat patients with inoperable, locally advanced NSCLC. The regime consisted of radiation doses of 300 cGy for 4 days every week for 4 weeks with a 2 week split in between. Each radiation dose was followed by an i.v. injection of cisplatin 6 mg/m² within 30 min. Hydration consisted on an oral fluid intake of 2 L only, enabling the patient to receive the treatment on an outpatient basis. Of 40 patients entered into the study, 37 were evaluable for toxicity and 33 for response. Overall response rate was 65% and complete response rate 22%. Median duration of local control was 7 months. The majority of all patients (76%) eventually progressed at the primary tumor site, while in 16 patients relapse occurred in distant sites first. Median duration of overall survival was 10.5 months, whereas that of complete responders was 29.5 months. Generally, acute side effects were transient and did not require discontinuation of treatment. One patient presented with thrombocytopenia 4 weeks after treatment had been finished. His death of cerebral bleeding was likely to be related with his therapy-resistant malignancy. Of late side effects three patients showed disabling symptoms consisting of uncontrollable pulmonary infections in the presence of tumor in two patients, one patient had radiation myelopathy and another experienced vertebral collapse with distal paresis. The combination of radiation and daily low-dose cisplatin is a tolerable treatment modality with most benefit for patients reaching a complete remission. Intensification of the regime is being planned in those patients with inoperable, locally advanced squamous cell lung cancer to reach a complete remission.

Radiotherapy, Cisplatin, Lung cancer, Radiosensitizer.

INTRODUCTION

For limited NSCLC, surgery is considered the primary treatment. The 5-year survival rate of patients with pathological Stage I disease is approximately 50%.1,12 Unfortunately, after completion of surgical staging fewer than 20% fall into this category. The 5-year survival rate in Stage II and III disease is very poor, because of local relapses or distant metastases. In these patients radiotherapy still serves an important role, whereas chemotherapy is considered to be ineffective. With the tumor confined to the chest, irradiation with curative intent can eradicate loco-regional disease and survival can be adequately prolonged.1,12 A small percentage of patients may even be cured. Also, this treatment modality can alleviate distressing symptoms caused by the intrathoracic tumor.7

Many radiotherapy studies have focussed on the improvement of loco-regional tumor control in NSCLC by prospective or retrospective clinical trials analyzing the influence of several variables, such as the total dose of irradiation, the number of fractions, the dose daily administered, continuous vs. split-course irradiation or the volume treated. Nowadays, it is apparent that doses of at least 50 Gy are required to obtain optimal intrathoracic tumor control, an important condition yielding a clear increase in the number of patients surviving. Perez,7 for the Radiation Therapy Oncology Group, has reported a 3-year survival rate of 20% for patients achieving a complete remission compared with less than 10% for those who had a partial remission or did not respond. In a radiotherapy study by the Veterans Administration Lung Group complete responders had a 50% probability to be

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alive at 2 years, whereas less than 25% of partial responders and none of the patients without a response were expected to be alive at that time point. Also Schaake-Koning et al. in a Dutch study very nicely showed that local control was related to survival and that better survival results were correlated with a high irradiation dose.

Another interesting area in the improvement of loco-regional control of NSCLC is the combination of irradiation with electron-affinic hypoxic-cell sensitizers, such as misonidazole, or with antitumor agents known for radio-enhancing properties, such as cis-diaminedichloroplatinum(II) (cisplatin). In contrast with in vitro data, for misonidazole combined with radiotherapy, randomized trials unfortunately failed to demonstrate clinical benefit. The potentiation of the effect of ionizing irradiation by cisplatin has been shown in several experimental murine tumors in vivo, with the drug administered either immediately before or after the radiation dose. This observation supplied the rationale for introduction of the combined treatment into the clinic, but experience in patients is thus far limited.

For several years, our group has been studying the combination of radiotherapy and daily low-dose cisplatin in patients with locally advanced solid tumor types including head and neck cancer, esophageal cancer, and NSCLC. In our feasibility study it was demonstrated that the daily administration of cisplatin at a dose of 8 mg/m² i.v. within 30 min after each radiation session resulted in impressive myelosuppression. With reduction of the dose to 6 mg/m² i.v. a combined modality split-course regimen was designed, which was tolerable and could be given at an outpatient basis. In the present investigation the regimen was studied in patients with inoperable, locally advanced NSCLC in an attempt to further improve loco-regional control, duration of remission and length of survival without increasing side effects.

METHODS AND MATERIALS

From September 1982 until September 1985 patients with inoperable, or unresectable NSCLC (T1N2, T2N0-2, T3N0-2) were entered into the study. Histology was proven to be squamous cell carcinoma, adenocarcinoma or large cell undifferentiated carcinoma. Eligibility criteria included a WHO performance status of 0 to 2, age below 75, a life expectancy of more than 3 months, a creatinine clearance of ≥60 ml/min, absence of chronic obstructive pulmonary disease (FEV₁ > 1 L), no prior chemo- or radiotherapy, no evidence of distant metastases, no pleural or pericardial effusions. Pretreatment screening tests included a physical examination, full blood and urine analysis, a chest X ray, a computerized tomography (CT) of the chest, abdomen and brain, bronchoscopy with washes and biopsies, a bone isotope scan and a pulmonary function test. During treatment, physical examination and blood chemistry profile including creatinine clearance were performed weekly, while serum creatinine and blood cell counts were assessed twice a week. Tumor response was determined by the pretreatment investigations mentioned above at the end of treatment, 6 weeks thereafter and repeated preferably 4 times each year. Therapeutic responses were defined according to WHO criteria. Duration of responses (complete and partial) and survival were recorded from the first day of treatment and calculated according to the Kaplan-Meier approach. Toxicity was recorded according to the WHO recommendation for grading of acute and subacute side effects.

Treatment consisted of radiotherapy in one daily fraction of 300 cGy 4 times a week for 4 weeks with a 2-week split in between. The total radiation dose was 48 Gy. A 4 MeV linear accelerator was used and beam portals included all areas of parenchymal involvement, the ipsilateral hilar lymph nodes and the entire mediastinum with at least 2 cm margin. No attempt was made to shield the spinal cord in the course of radiotherapy. Within 30 min after each radiation dose an i.v. injection of cisplatin 6 mg/m² in 60 ml normale saline was administered without pre- or posthydration. The patients had to provide for a daily oral fluid intake of at least 2 L. Treatment was given on an outpatient basis. Metoclopramide was prescribed in case of nausea. A rising serum creatinine or severe vomiting were reasons for admission into hospital to supply adequate i.v. hydration (4 L of normal saline on treatment days).

RESULTS

A total of 40 patients were entered into the study of which one was not eligible because of distant metastases at presentation. Two other patients were not evaluable for toxicity, because one patient eventually received radiotherapy alone and the other had to discontinue treatment due to severe non-treatment related pectoral angina. Characteristics and toxicity of 37 patients are shown in Table 1. Most patients presented with squamous cell cancer. Four patients could not be evaluated for response because of extensive local fibrosis. Of the remaining 33 patients 8 achieved a complete remission, 16 a partial remission, 7 patients had stable disease, and in 2 patients the disease was progressive. The overall response rate of 37 patients was 65% with 22% complete responders. Although not all patients were evaluable for the effect of treatment, in most of them the initial site of progression could be located. Presently 2 patients have not progressed. Median time of local control was 7 months. First relapse occurred at the primary tumor site in 19 patients and in distant sites in 16 patients. The majority of all patients (76%) eventually had progression of the primary tumor at the time of death. Distant metastases were localized in lymph nodes (2), lungs (3), kidney (1), lungs and kidney (1), adrenal gland (2), bone (3), liver (1), pericardium (1) and brain (2). Median duration
Table 1. Patients’ characteristics and treatment toxicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F: 31/6</td>
<td>37</td>
</tr>
<tr>
<td>Median age in years: 56 (range 34–72)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>24</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Large cell undifferentiated carcinoma</td>
<td>8</td>
</tr>
<tr>
<td>Hematologic toxicity (nadir) WBC</td>
<td></td>
</tr>
<tr>
<td>count ($\times 10^9$ cells/mm$^3$)</td>
<td></td>
</tr>
<tr>
<td>Grade 1 (3.0–3.9)</td>
<td>13</td>
</tr>
<tr>
<td>Grade 2 (2.0–2.9)</td>
<td>9</td>
</tr>
<tr>
<td>Grade 3 (1.0–1.9)</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count ($\times 10^9$ cells/mm$^3$)</td>
<td></td>
</tr>
<tr>
<td>Grade 1 (75–99)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2 (50–74)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3 (25–49)</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal toxicity nausea and</td>
<td></td>
</tr>
<tr>
<td>vomiting</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>6</td>
</tr>
<tr>
<td>Grade 2</td>
<td>22</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td></td>
</tr>
<tr>
<td>Grade 1 ($1.26–2.5 \times N^*$)</td>
<td>8</td>
</tr>
<tr>
<td>Grade 2–4</td>
<td>0</td>
</tr>
</tbody>
</table>

* Value at start of treatment.

of overall survival was 10.5 months, whereas that of complete responders was 29.5 months.

In general, toxicity was mild and consisted of myelosuppression, swallowing problems with nausea and vomiting and renal toxicity (Table 1). Hematologic toxicity and gastrointestinal side effects were transient and never caused treatment delay. One patient had thrombocytopenia occurring at 4 weeks after treatment had been finished and died of cerebral bleeding. As the patient’s tumor did not respond, low platelet counts may have been related to his malignancy. Most patients could be treated as an outpatient basis. A few patients with swallowing problems had to be admitted into hospital for parenteral fluid substitution to prevent nephro-toxicity. Of 8 patients with a slight increase of serum creatinine 4 returned to normal after completion of treatment. Late side effects occurred as there were pneumonitis (8 patients), bullous lesions within a fibrotic area (5 patients), radiation myelopathy (1 patient), and vertebral collapse with distal paresis without evidence of tumor (1 patient). Two patients with bullous degeneration had uncontrollable infections in the presence of residual tumor. Generally, pneumonitis did not cause symptoms or require medication and could be detected only by a CT-scan.

**DISCUSSION**

This study is the first reported involving radiotherapy combined with daily low-dose cisplatin in patients with inoperable, locally advanced NSCLC performed in one single institution. The combination was investigated in 37 patients and appeared to induce a high overall response rate of 65%. Those achieving a complete remission experienced a longer duration of survival as compared to patients with a partial or no response. However, the number of complete responders is still limited (22%) and 43% of the patients had a relapse in distant sites first. The treatment was well-tolerated and could be administered on an outpatient basis in most patients.

Experimental data have clearly shown that cisplatin has the ability to enhance the effect of ionizing radiation in some tumors. Several treatment schedules with cisplatin given either before or immediately after radiation, appeared to improve the therapeutic ratio. In our patient we injected cisplatin within 30 min after radiotherapy to optimally inhibit sublethal damage repair by the active free platinum species. However, by employing the inverse sequence therapeutic effects may even be increased by the potential hypoxic cell radiosensitization due to the electron affinity of platinum compounds.

The treatment results, although still from a small group of patients, indicate that they are at least similar to those obtained with radiotherapy alone. For instance, in a comparable group of patients treated with radiation doses of 50 to 60 Gy, Perez reported a complete response rate of 25% and an overall response rate of 65%. Median overall survival was approximately 11 months, while complete responders had a median survival period of approximately 18 months. The number of patients experiencing late side effects with disabling symptoms was 7%. Whether the combined modality approach will yield improved treatment results in NSCLC is the main objective in an ongoing randomized EORTC trial studying tumor response and toxicity after radiotherapy alone as compared with radiotherapy combined with cisplatin given either weekly (30 mg/m$^2$) or daily (6 mg/m$^2$).

The intrathoracic failure rate in our patients was 76%. Perez reported a failure rate of 54% in patients treated with radiation doses of 50 to 60 Gy and 25% also had metastatic lesions. In the study of Schaake-Koning et al., 65% of patients with inoperable, localized NSCLC treated with high-dose radiation (50 Gy) eventually presented with a local recurrence, whereas 26% also showed distant metastases. In a retrospective study by the Veterans Administration Lung Group in a large number of patients treated with radiation for NSCLC confined to one hemithorax the pattern of failure appeared to depend on the histologic subtype. Patients with adenocarcinoma and large cell carcinoma had a tendency to exhibit disseminated disease, whereas patients with squamous cell carcinoma presented with recurrence of local disease first.

Regional control of inoperable, locally advanced NSCLC significantly improves survival. Innovative treatment schedules should be developed in an attempt to obtain a higher number of complete remissions. Importantly, only patients without distant metastases
should be selected for such regimens requiring extensive
diagnostic procedures. Whether histologic subtypes with
a tendency to disseminate should be excluded from in-
tensive local therapy is a point of discussion. Our treat-
ment results obtained with radiotherapy and daily low-
dose cisplatin have stimulated us to design a new regi-
men in which cisplatin 6 mg/m² i.v. is administered 30
min before the radiation dose (total dose 52.5 Gv in a
continuous course schedule) in patients with inoperable,
locally advanced squamous cell cancer of the lung with
the aim to further improve survival in this common can-
cer type.

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