Daily Cis-dichlorodiammineplatinum (II) as a Radio-enhancer:  
A Preliminary Toxicity Report

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Summary. A combination of radiotherapy and daily administration of cis-dichlorodiammineplatinum (II) (CDDP) was given to six patients with locally advanced solid tumors including regional lymph-node metastases. Four of these patients had esophageal cancer (two with supravaculicular lymph-node metastases), one patient had oropharyngeal cancer (T4N1M0), and one had recurrent cancer of the tongue with involvement of the skin of the neck. Radiotherapy in fractionated daily doses was given to three patients and the other three received superfractionated (two fractions/day) doses; CDDP was given within 15 min after radiotherapy at a dose of 8 mg/m² for fractionated and 4 mg/m² for superfractionated treatment. Evaluation of response in irradiated fields showed complete tumor control, as judged from histological examination in three patients, partial tumor regression in two (recurrent carcinoma of the tongue), and no response in one. One patient showed tumor progression in irradiated fields 7 weeks after treatment and two developed distant metastases. Due to severe leukopenia (<2,000/mm³) occurring after the 3rd week of treatment, treatment was postponed in one patient and discontinued in two. Sepsis occurred in two patients and two patients developed severe thrombocytopenia (25,000/mm³ to 44,000/mm³). All patients needed red cell transfusions during therapy. Serum levels of sodium, potassium, calcium, and magnesium dropped in all patients, whereas renal function was stable. Only one patient showed severe gastrointestinal toxicity, expressed in vomiting and diarrhea. These preliminary data warrant further evaluation of this regimen, but it is clear that the treatment requires intensive supportive care.

Key words: Head and neck cancer - CDDP - Radio enhancement - Toxicity

Introduction

In all probability, cis-dichlorodiammineplatinum (II) (CDDP) inhibits DNA synthesis by the formation of cross-links with the DNA molecule (Heinen et al. 1976; Rosenberg 1975). From a theoretic point of view, the combination of CDDP treatment and radiotherapy for the treatment of cancer seems attractive. Indeed, experimental studies have shown in a variety of tumors that the combination of CDDP and radiotherapy has a synergistic effect (Douple et al. 1977; Douple et al 1979; Douple et al. 1979; Soloway et al. 1979; Wodinsky et al. 1974; Yuhas et al. 1979). Synergism has also been shown for some normal murine tissues (Burholt et al 1979; Douple et al. 1979; Dritschilo et al. 1979; Luk et al. 1979). The optimal timing of CDDP in relation to radiotherapy is not known; enhancement of the radiation effect by CDDP has been seen whether the drug was given before or after radiotherapy.

Recently, Creagen et al. (1981) described three patients with advanced head and neck cancer given CDDP combined with radiotherapy and Reimer et al. (1981) reported on 13 patients with metastatic solid tumors who were treated with CDDP during palliative radiation therapy. Toxic effects were described as moderate and synergism as to the anti-tumor effect was suggested for patients with invasive melanoma (Reimer et al. 1981). These papers have been the only reports available on treatment with CDDP and radiotherapy. The present communication gives preliminary data on the concurrent use of daily CDDP and radiotherapy in six patients. Impressiv therapeutic responses have been observed, but the regimen appeared to be extremely toxic.

Materials and Methods

Since August 1980, six patients have been treated with a combination of radiotherapy and CDDP. All of them suffered from locally advanced inoperable solid tumors including lymph-node metastases
There were four patients with esophageal cancer, two of them with supravacular LNM, one patient with oropharyngeal cancer, and one with residual cancer of the oral tongue and cutaneous involvement. Toxicity was assessed and antitumor effect was evaluated in biopsy specimens. For radical radiation therapy, which was attempted for each patient, use was made of a 4-6 MeV linear accelerator with an angled cumulative dose of a dose 6,000 rad delivered over 6% to 7% weeks. Relatively large multiple fields were chosen and the daily dose was 180 rad when conventional fractionation was used. With superfractionated schemes, all fields were treated per fraction and 125 rad was delivered to the tumor volume per fraction, irrespective of the volume. Two such fractions were used to deliver 250 rad/day to the tumor, with a minimum interval of 3 h between the fractions. Within 15 min after radiotherapy CDDP was given at a dose of 4 mg/m² twice a day for superfractionated radiotherapy (schedule A) and in a dose of 8 mg/m² once a day for conventional fractionated radiotherapy (schedule B). A 3-4 l/day hydration schedule with saline was given throughout the treatment period. When diarrhea was less than 600 cc/6 h mannitol was used, and, if necessary, low doses of Furosemide (5-10 mg) were given in addition. All patients received 20 mg metoclopramide three times a day.

Results

A brief case report will be presented for each of the six patients in this series. It should be noted that cisplatin administered alone in the fourth, fifth, and sixth patients prior to the combined treatment, was not effective. Table 1 summarizes their characteristics.

Case 1

A 53-year-old female with squamous-cell anaplastic (G3) carcinoma of the thoracic esophagus with Horner's syndrome and supravacular nodal metastases of approximately 5 cm in (maximal) diameter was initially given CDDP 100 mg/m² i.v., which led to minor regression of the metastases. Schedule B was started 2 weeks later (total 4,015 rad). After 23 days of combined therapy, this treatment had to be discontinued because leukopenia developed (1,900/mm³) as well as serious side effects consisting of nausea, vomiting, and diarrhea. Immediately after termination of the therapy, there was a complete regression of the supravacular LNM, but 3 weeks later extensive liver metastases became manifest. The patient died of hepatic failure 6 weeks after discontinuation of the radiotherapy and with the supravacular LNM still in complete remission. Autopsy was refused.

Case 2

This was a 61-year-old male with a poorly differentiated (G3) adenocarcinoma of the mid and lower thoracic esophagus (T₃N₀M₀). Three weeks after he started on schedule B, treatment had to be interrupted because of leukopenia (1,900/mm³) and thrombocytopenia (44,000/mm³). Four weeks later the treatment was resumed and could be completed without any further signs of toxicity. A total dose of 6,090 rad was delivered in 30 fractions, but in 75 days with interruptions. Four weeks after the end of therapy, bone and liver metastases became evident, but local control was found on esophagoscopy and biopsy. Seven weeks after the treatment, esophagoscopy was repeated and a biopsy reported as positive indicating local failure. The patient died 3 months after completion of the radiotherapy.

Case 3

A 71-year-old male with a moderately differentiated (G2) squamous-cell carcinoma of the lowest one-third of the esophagus showed mediastinal and supravacular LNM after 3 weeks on schedule B (3,060 rad in 17 fractions). The therapy was discontinued because of thrombocytopenia (25,000/mm³). At that time, the supravacular LNM were in regression. Tracheostomy was necessary because of obstruction of the upper bronchial tree by mucus formation. Recurrent attacks of pneumonia occurred as well as sepsis. After recovery, the patient refused further treatment. Two months after the termination of the therapy he died. At autopsy, there was still a detectable tumor in the irradiation field and an extensive tumor mass was also found outside the radiation field in the lower part of the mediastinum, possibly due to LNM. The radiation dose had, however, been inadequate.

Table 1. Patient characteristics, treatment results, and radars

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Site of carcinoma</th>
<th>Histological diagnosis</th>
<th>Treatment schedule</th>
<th>Response</th>
<th>WBC nadir</th>
<th>Thrombocyte nadir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>Esophagus</td>
<td>Squamous cell</td>
<td>B</td>
<td>PR (7)</td>
<td>1,900</td>
<td>136,000</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>Esophagus</td>
<td>Adenocarcinoma</td>
<td>B</td>
<td>PR</td>
<td>1,900</td>
<td>44,000</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>Esophagus</td>
<td>Squamous cell</td>
<td>B</td>
<td>PR</td>
<td>4,000</td>
<td>25,000</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>Esophagus</td>
<td>Squamous cell</td>
<td>A</td>
<td>CR</td>
<td>3,000</td>
<td>151,000</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>Oropharynx</td>
<td>Squamous cell</td>
<td>A</td>
<td>CR</td>
<td>2,300</td>
<td>134,000</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>Tongue (recurrent) with skin involvement</td>
<td>Squamous cell</td>
<td>A</td>
<td>PD</td>
<td>300</td>
<td>104,000</td>
</tr>
</tbody>
</table>

A = superfractionated treatment; B = fractionated treatment
PR = partial remission; CR = complete remission; PD = progressive disease
Case 4

In a 65-year-old female with an obstructive, moderately differentiated (G2-G3) squamous-cell carcinoma of the cervical esophagus (T3N0M0) treatment was started with a single dose of CDDP (100 mg/m²). There was no evidence of tumor response. Three weeks later, combined therapy was started and schedule A was maintained until a cumulative dose of 6,000 rad was reached. Because of edema of the trachea, a temporary tracheotomy was required and the esophagus had to be dilated several times because of strictures. During treatment the patient’s condition deteriorated badly and sepsis developed. However, she recovered gradually. Except for anemia, there were no signs of hematologic toxicity. At the time of writing, 17 months after the end of therapy, the patient is in excellent condition and still in a complete, histologically proven remission.

Case 5

A 43-year-old female with a moderately differentiated squamous-cell carcinoma of the oro/hypopharynx and extensive infiltration into the tongue (T4N1M0) initially received a single dose of CDDP (100 mg/m²). No evident tumor response was noticed. Three weeks later, combined therapy was started with schedule A up to a cumulative dose of 6,500 rad. Except for moderate anemia and severe mucositis, no serious side effects were observed. A tracheotomy was temporarily necessary. At the time of writing, 18 months after termination of the therapy, the patient is in excellent condition and still in histologically proven, complete remission.

Case 6

This was a 64-year-old male with recurrent, moderately differentiated squamous-cell (G2) carcinoma of the oral tongue with skin involvement of the neck, after previous surgery and radiotherapy for a T3N1 carcinoma of the mobile tongue. Three weeks before the institution of combined therapy, treatment was started with a single dose of CDDP (100 mg/m²); no tumor response was noticed. One week before schedule A had been completed (total dose 6,000 rad), CDDP was stopped because of leukopenia (500/mm³). Sepsis occurred but was treated successfully and the white blood cell count returned to normal. The tumor did not respond to therapy and the patient died 7 months after the start of therapy.

In all six cases anemia requiring red cell transfusions occurred and the serum levels of sodium, potassium, calcium, and magnesium dropped. Serum creatinine and creatinine clearance did not change significantly.

Discussion

Extensive information about the interaction between radiotherapy and CDDP, collected in animal models, indicates that there is a synergistic effect on tumor tissue as well as in normal tissues; CDDP has been applied prior to and after radiation, but little is known about the effect in patients with solid tumors (Creagen et al. 1981; Reimer et al. 1981). Creagen et al. (1981) stressed the extreme toxicity, especially gastrointestinal, in excess of that normally seen with either modality alone. These authors used a CDDP dosage of 30 mg/m² given over a period of 1 h on days 2 and 12 and two courses of 3,000 rad each, followed by a treatment-free interval of 3 weeks. Reimer et al. (1981) used 20 to 50 mg/m² weekly, administered in 30 min with 1 l hydration and 12.5 g mannitol before CDDP. Besides gastrointestinal intolerance (12/13 patients), renal toxicity occurred in 3/13 patients and led to dose modifications. Severe leukopenia developed in three patients.

Neither of these reports mentions the exact timing of CDDP administration in relation to radiation. In the present pilot study, we combined CDDP with radiotherapy on a daily basis. Besides introducing fractionated daily administration of CDDP in three patients, we also applied a superfractionated schedule in three other patients, who were given the drug twice daily after the radiation dose. For the preliminary report, we evaluated toxicity and antitumor effect in these six patients. With respect to the selection of the proper timing of the CDDP dose in relation to the radiation dose, we introduced the postradiation administration of the drug on a pharmacokinetic basis because we assumed that the free platinum (not bound to plasma proteins) is the active species and wished to exploit the rapid plasma decay of free platinum. At a daily CDDP dose of 8 mg/m², the most prominent toxicity was myelosuppression, which occurred 3–4 weeks after initiation of therapy. However, the present findings clearly show that the daily administration of ultra-low dosages may lead to severe bone marrow toxicity. Evidently, cytostatic levels of platinum are reached and this prevents repopulation of the bone marrow cells. Electrolyte disturbances, including hypokalemia, hypomagnesemia, and/or hypomagnesemia, developed in all six patients.

It is of interest that serum creatinine and creatinine clearance remained stable throughout the treatment period. In contrast to the two above-mentioned pilot studies, gastrointestinal toxicity was unexpectedly low in the present study (only one patient showed severe GI toxicity), probably due to the low dose of CDDP. None of the patients complained of clinical hearing loss and no serious neurological complications were observed.
A daily superfractionated schedule of CDDP without radiation therapy has not been evaluated; such an evaluation would obviously create ethical problems because one would not expect this particular schedule to lead to a better therapeutic response than the conventional schedules. As far as the antitumor effect of cisplatin is concerned, no schedule dependence has been observed, although continuous administration of CDDP for 5 days resulted in less toxicity than short-term infusion is known to give.

In the present study the antitumor effect in irradiated areas was encouraging, particularly in patients 4 and 5, who may well have been cured. Both had large local tumors, which are rarely cured by radiotherapy alone. With respect to antitumor activity, these results seem to support the occurrence of synergism with the schedules applied. Our findings warrant further studies with these treatment schedules. We are continuing the evaluation of schedule A in patients with squamous-cell carcinoma in the head and neck area and in the bronchus, but the intensity of patient care required precludes large-scale studies in the usual medical oncology unit.

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Received July 16, 1982/Accepted September 30, 1982