Study of *Cis*-Diammine-Dichloro-Platinum in Advanced Soft Tissue Sarcoma*†

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1. BACKGROUND AND INTRODUCTION

Protocol 62761 of the Soft Tissue Cooperative Group is presently studying 2 combination chemotherapy regimens consisting of adriamycin, DTIC, cyclophosphamide and vincristine in patients with advanced soft tissue sarcoma. In the first arm (S1) the four drugs are given simultaneously on day 1, while DTIC is continued during 5 days. In the second arm (S2) adriamycin and DTIC are given simultaneously without cyclophosphamide and vincristine. The latter 2 drugs are alternated with the former 2 drugs every 4 weeks. The most active drugs in the treatment of soft tissue sarcomas are adriamycin and DTIC. The combination of these 2 drugs has proven to be more effective in soft tissue sarcoma than each of the 2 drugs given as a single agent. Vincristine and cyclophosphamide are quite ineffective in soft tissue sarcomas when given as single agents. Recently, *cis*-diammine-dichloro-platinum (*cis*-DDP) has proven to be effective in several solid tumors such as testicular carcinoma, ovarian cancer, bladder cancer and possibly in head and neck tumors as well [1-4]. The only data available on the effect of *cis*-DDP in soft tissue sarcoma consist of 5 available patients in a phase I study [2]. No response was observed in these patients. The Soft Tissue Sarcoma Group offers an excellent patient population to perform a phase II trial of *cis*-DDP in soft tissue sarcoma. This phase II study can be performed in patients who go off study in the protocol for advanced sarcoma (62761) and will give us information on the response rate of this tumor within 6 months from now. In case *cis*-DDP would prove to be active in soft tissue sarcoma our next step will be to initiate a protocol in advanced sarcoma including this drug in combination regimens. As all the investigators participating in the study for advanced soft tissue sarcoma are internists we feel that it is justified to introduce this toxic drug into the Soft Tissue Sarcoma Cooperative Group.

2. PURPOSE OF THE STUDY

(a) The main purpose will be to determine objective tumor response rate and duration of response to DDP in patients with advanced soft tissue sarcoma who have failed all treatment presently available.

(b) To determine the morbidity of *cis*-DDP treatment in this group of patients.

3. SELECTION OF PATIENTS

3.1 Conditions for patient eligibility

Patients with advanced soft tissue sarcoma who have failed on conventional treatment. This includes patients leaving protocols 62761 and 62771 because of progression and patients...
who are not eligible to enter 62761. The patient should have a measurable lesion with progression during the 4 weeks prior to treatment.

3.2 Conditions for patient exclusion

Patients 20 yr old or younger, patients above 70 yr and patients with abnormal kidney function: creatinine clearance below 80! Unfavourable, haematologic status; WBC below 3000/mm³ and platelet count below 150,000/mm³, cytostatic agents during the previous four weeks, performance status according to Karnofski under 50, central nervous system lesions, intercurrent infection and overt psychosis or marked senility.

4. DESIGN OF THE TRIAL

All patients will receive the same treatment schedule consisting of DDP in dextrose 5% infusion containing mannitol. The infusion will be given over 3 hr. If during the 1st course 100 mg/m² DDP is tolerated without toxicity, the dose will be increased to 120 mg/m² in the subsequent courses. This treatment will be repeated every 3 weeks. The response will be evaluated after the second course. If at 6 weeks there is tumor regression or no change, treatment will be continued until progression. If there is progression at 6 weeks the patient will go off study. Patients responding to treatment must be followed to progression and to death whenever possible.

5. THERAPEUTIC REGIMENS AND TOXICITY

5.1 Prior to the DDP infusion the patient should receive 1 l. of saline over a period of 4 hr. Cis-DDP 100 mg/m² will then be given in 1 l. dextrose 5% containing 37.5 g of mannitol over a 3 hr period. Diuresis should be maintained by giving an additional 3-liter saline infusion over the following 24 hr. In case the urine output is insufficient (<600 cm³ per 6 hr) furosemide 20–40 mg/day should be added to the regimen. Thus, careful monitoring the urine output is essential! This treatment will be repeated every 3 weeks. If during the 1st course 100 mg/m² DDP is tolerated without toxicity the dose of DDP will be increased to 120 mg/m² in the subsequent course. The patient will be evaluated after 2 courses. The treatment will be continued until progression in case of no change or regression after 6 weeks. In case of progression at 6 weeks the patient will go off study.

5.2 DDP toxicity

The most important toxicity is renal failure. However, a good renal function prior to treatment and an adequate urine output during the 24 hr of treatment makes this complication unlikely [2, 5]. Auditory abnormalities consisting of a high pitch hearing loss may occur. Myelosuppression, reaching its nadir at day 10–14, is often seen but is not severe. Anaphylactic reactions are rare. Antiemetics should be given but are only slightly effective. In case of infectious complications following the treatment, gentamycin should be avoided whenever possible as there is probably a cumulative toxicity to the kidney. The same is true for damage which may be caused to the auditory nerve by gentamycin. In case gentamycin has to be given, never add cephalothin to this regimen as this combination is still more toxic to the kidney. Serious nephrotoxicity has been observed with this combination [6]. In case the serum creatinine increases during treatment to a level above 1.2 mg/100 ml the kidney function will, in most cases recover within 3 weeks. If, however, at 3 weeks the serum creatinine is still above 1.2 mg/100 ml the next dose should be postponed for a maximum of one week (4 weeks after previous dose). If at 3 weeks after the previous course the WBC count is below 3000 or the platelet count is below 150,000 the treatment should be postponed as well for 1 week. In case treatment has to be postponed for more than 1 week the patient should go off study due to toxicity.

6. REQUIRED CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP

6.1 Age, sex, case history and duration of symptoms (specify), date of clinical and pathological diagnosis and how this was established, prior treatment (data and methods). The physical examination should include: height and weight, the Karnofski index and exact description and measurement of the measurable parameters.
6.2 The minimal laboratory studies required are: complete bloodcount, creatinine clearance, liver function tests consisting of bilirubine, alkaline phosphatase, gammaglutamyl trans-peptidase, SGOT, SGPT and if possible cholinesterase. Furthermore, urinanalysis should be done. Because of the possible otoxicity an audiogram should be performed prior to treatment as well. Radiological examination should include a chest X-ray and a skeletal survey. An isotopic bone scan is optional.

6.3 Follow-up. Before each treatment course the morbidity of the previous course should be registered. Furthermore, a clinical examination, blood investigations, and evaluation of the Karnofski index are required. An audiogram will be repeated after the second course. Any unexpected side effects of treatment should be reported immediately to the study coordinator. A clear description of the tumor response is required prior to the third course.

7. CRITERIA OF EVALUATION

Patients are considered evaluable if they have been treated with a minimum of 2 courses.

7.1 Complete remission

Disappearance of all symptoms and signs of soft tissue sarcoma for a minimum of 3 weeks.

7.2 Partial remission

Significant decrease in size in at least 50% of all lesions for a minimum of 3 weeks while the remainder are static. Such a decrease is defined as a reduction by 50% of the product of the two largest perpendicular tumor diameters. Changes in body chemistry and improvement in hemopoiesis cannot be construed as criteria of objective remission.

7.3 Stable disease

Less than 50% reduction in the product of largest perpendicular diameters of measurable lesions or less than 25% increase in any of the measurable lesions. No appearance of any new lesion.

7.4 Progression

Increase of more than 25% in the product of the largest perpendicular diameters of any lesion. Also, appearance of any new lesions regardless of the response of other lesions.

7.5 Early death

Death occurring during the first three weeks due either to tumor progression or drug toxicity.

8. REGISTRATION

A patient is registered after the local pathology review by telephoning to the E.O.R.T.C. Data Center, phone: Brussels: 538.65.33 or by telex 22.773 from 9.00 a.m. to 5.00 p.m., Monday–Friday. The following information is requested:

1. protocol number (62781),
2. name of the institution,
3. name of the patient,
4. histological type,
5. name of the responsible investigator.

9. SUBMISSION OF FORMS

All forms are to be sent in duplicate to the E.O.R.T.C. Data Center, Institut Jules Bordet, 1, Rue Héger Bordet, 1000 Bruxelles, Belgium.

The schedule for submission of forms is as follows:

1. On-Study form

Send within one week of the patient’s entry on study, 1 page.

2. Chemotherapy form

Send after completion of each 2 cycles of DDP, 1 page.

3. Flow-sheet

The first flow sheet should be filled out prior to the first cycle of chemotherapy and sent with On-Study form. It should also be filled out at 6 weeks and thereafter every 12 weeks as long as the patient remains on-study. Also immediately upon progression, 1 page.

4. Measurement form

Send with on-study, at 6 weeks and every 3 weeks thereafter as long as the patient remains on-study. Also immediately upon progression.

5. Summary form

To be sent upon progression or death, whichever comes first.
10. STATISTICAL CONSIDERATIONS

The lowest limit of therapeutic activity considered to be of interest is a response rate of 20%. Twenty-nine patients will be entered on study and the drug rejected from further study if 3 or fewer responses are obtained. If no response has been obtained in the first 19 patients treated the study will be stopped. This plan insures that if the drug has a response rate of at least 25% the probability of rejecting the drug from further study is approximately 0.05.

11. ADMINISTRATIVE RESPONSIBILITY

This study is a joint effort among the investigators working in the E.O.R.T.C. Soft Tissue Sarcoma Cooperative Group. The secretary of the group will evaluate the clinical data of patients while the statistical analysis will be performed by Dr. Richard Sylvester. Dr. Sylvester can be reached at the Data Center.

The address of the Secretary Dr. H. M. Pinedo is: Oncology Unit, Department of Internal Medicine, University Hospital, Utrecht, The Netherlands. Telephone: 030-372202.

REFERENCES