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Alternatives to CYVADIC combination therapy of soft tissue sarcomas*

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Summary. The CYVADIC combination has been the preferred treatment for soft tissue sarcomas for the last 10 years. Other combination therapies are necessary, because the remission rate achieved with CYVADIC is only 30%. Alternative therapies for these tumors are combinations including *cis*-platinum, ifosfamide, epipodophyllin, and high-dose methotrexate. Our therapeutic results with combinations of *cis*-platinum and ifosfamide are comparable to those achieved with CYVADIC. However, the side-effects, such as nausea, vomiting and fatigue, of *cis*-platinum used in the palliative treatment of these tumors are intolerable for many patients. A combination of adriamycin and ifosfamide, which leads to a higher remission rate of 44% and has lower toxicity than CYVADIC, is giving encouraging results.

For most oncologists CYVADIC combination therapy is the preferred therapy for the treatment of soft tissue sarcomas. This combination was developed and introduced in 1975 by Gottlieb et al. of the Southwest Oncology Group [6]. They reported a remission rate of 55%, with 15% complete remissions. The efficacy of this drug regimen was confirmed by many other groups, but the response rate was considerably lower, closer to 30% [7–9]. One reason for these different results may be the great variation in the histological entity of soft tissue sarcomas with variable sensitivity to chemotherapy [4, 5, 10]. Using the CYVADIC combination in our clinic with the same dosages, method of administration, and treatment intervals as reported by Gottlieb, we have found (analyzed retrospectively) a response rate of exactly 33% in 48 sarcoma patients.

In an attempt to improve the chemotherapeutic results in patients with soft tissue sarcomas, we have investigated the combination of *cis*-platinum and ifosfamide in a prospective phase II study. These two drugs were selected as alternatives to the CYVADIC therapy because in 1978 and 1979 *cis*-platinum was new and available and had been shown to be active against many tumors [3]. This was particularly true for testicular cancer and in some cases when patients with soft tissue sarcomas had been preteated with CYVADIC and high-dose methotrexate [1, 7, 11].

Abbreriations: CR, complete remission; CYVADIC, cyclophosphamide; vincristin, adriamycin; DTIC, dacarbazin; DDP *cis*-platinum; IFO, ifosfamide; NC, no change; PD, progressive disease; PR, partial remission; SD, stable disease

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Materials and methods

Sixty-eight patients aged 20–72 years (mean 51 years) were included in a preliminary study with *cis*-platinum and ifosfamide. Their characteristics are shown in Table 1. Forty-one of the patients were male and 27, female. In this study the most frequent histological type was fibrosarcoma (23 patients), followed by leiomyosarcoma (17 patients).

The dosage regimen is shown in Fig. 1. The cytostatics were administered over 5 days. The hydration period, with a minimum of 3 l normal saline per day, and antiemetics were given 12 h before the cytostatics. The dose of *cis*-platinum was 20 mg/m^2 per day and of ifosfamide 1.5 g/m^2 per day. Mesna, as a bolus injection, was given before and 4 h and 8 h after the start of ifosfamide therapy. Each dose of mesna was calculated to be 20% of the ifosfamide dose. The infusion time for *cis*-platinum and ifosfamide was 4 h.

In a second study with adriamycin and ifosfamide we included 14 patients. Dosage regimen and method of administration are shown in Fig. 2. A dose of 50 mg/m^2 adriamycin was divided over 3 days and 7.5 g/m^2 ifosfamide was divided over 5 days. Ifosfamide was administered in combination with mesna as described above. The standard antiemetic drug was metoclopramide (1 mg/kg per 12 h) in Ringer's solution.

Table 1. Soft tissue sarcoma: *cis*-platinum/ifosfamide combination

Patients characteristics	
Number	68
Age (mean)	51
Male	41
Female	27
Fibrosarcoma	23
Leiomyosarcoma	17
Angiosarcoma	6
Rhabdomyosarcoma	4
Liposarcoma	4
Synovial sarcomas	3
Unclassified sarcomas	3
Mesothelioma	8

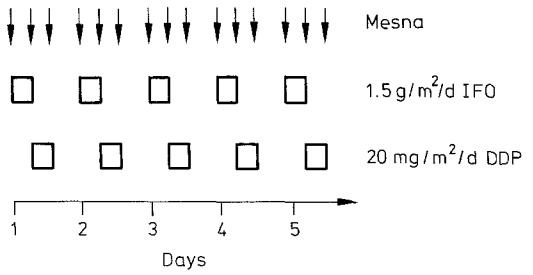

Fig. 1. Therapeutic regimen with *cis*-platinum and ifosfamide for disseminated soft tissue sarcomas

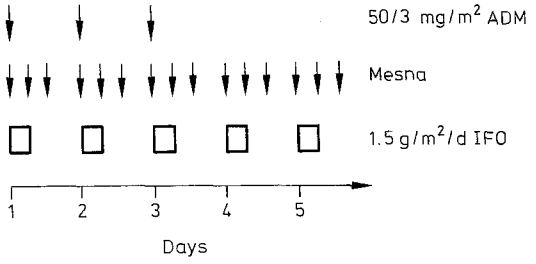

Fig. 2. Combination of ADM and IFO in treatment regimen for soft tissue sarcomas

Results

The results of the therapy with *cis*-platinum and ifosfamide are shown in Table 2. The remission criteria are the internationally accepted WHO criteria. The remission rate was 44%, with 10% of the patients achieving complete remission. In 30 patients there was no change in the disease after a minimum of 4 months, and in 8 patients the disease had worsened. The duration of complete remission lasted 12, 15, 16, 19 and 22 months, and in two patients the remission was complete after 22 and 27 months.

With this therapy the most prominent side-effects were nausea and vomiting, which were experienced by all patients. As rated by WHO criteria, 28 patients experienced grade III and 6 patients grade IV vomiting. Bone marrow toxicity was mild to moderate, with only six patients reaching grade II and two patients grade III. Seven patients developed fever after therapy and were treated with a combination of double – beta – lactam – antibiotics such as cephalosporins of the third generation and ureido-penicillins. In two of these seven patients the causative agents were identified in blood cultures as *E. coli* and *S. aureus*. All patients recovered from infection. There was no sign of renal toxicity due to *cis*-platinum as measured by serum creatinine, and no hematuria was observed.

In an ongoing study with adriamycin and ifosfamide, we have included to date 14 patients with disseminated or locally advanced histologically proved soft tissue sarcomas. The results are shown in Table 3. Complete remission has been achieved in three patients, and partial remission in seven patients. The disease is stable in three patients after 3, 7, and 10 months and one patient has worsened during treatment. The gastrointestinal side-effects in particular (nausea and vomiting) were considerably, less significant than with the *cis*-platinum/ifosfamide combination. Vomiting has not been observed, and nausea has been reported by only 7 of the 14 patients. Bone marrow toxicity

Table 2. Results with DDP and IFO in the treatment of disseminated soft tissue sarcomas

Total number	68	Percent of total
CR	7	10
PR	23	34
NC/SD	30	44
PD	8	12

Table 3. Results of ADM/IFO treatment of soft tissue sarcomas

Total number	14
CR	3
PR	7
NC	3
PD	1

is mild or moderate. In only two cases has the leukocyte count fallen below 2000 and the thrombocytes count below 70,000. Other side-effects, such as CNS disorders or hematuria, have not been observed. In a preliminary dose-finding study, we administered a dose of 7.5 g/m² ifosfamide over only 3 days, and two patients had CNS side-effects, exhibited as hallucinations in one case and stupor in the other.

Discussion

The side-effects of *cis*-platinum/ifosfamide combination chemotherapy most often noted were subjective. The cumulative toxicity was accompanied by a loss of appetite, sense of taste, and weight. In addition, anemia, fatigue, and a progressive deterioration in general well-being were observed. These side-effects could not be correlated to bone marrow toxicity, renal toxicity or vomiting.

This cumulative toxicity was mainly attributable to *cis*-platinum, the efficacy of which was questioned in the treatment of soft tissue sarcomas in EORTC study [8].

A group at the Royal Marsden Hospital has published good results obtained with high-dose ifosfamide alone [12]. Therefore, we began a new study with adriamycin, the most important drug in the CYVADIC combination, and ifosfamide.

The encouraging aspect of this adriamycin/ifosfamide combination is not the remission rate but its low toxicity. In particular, the emotionally stressful side-effects, such as vomiting and nausea, are much slighter than with the *cis*-platinum/ifosfamide combination. Vomiting was avoidable in all patients with the standard antiemetic metoclopramide, and nausea was experienced by 15% of the patients. The hematological toxicity was mild and hematuria was prevented by administration of mesna.

Conclusion

The CYVADIC regimen still remains the standard therapy of soft tissue sarcomas [9, 12]. All other therapeutic regimens must be compared with this combination. *cis*-platinum and ifosfamide may be as effective as CYVADIC but

the toxicity is higher, particularly after four or more therapy cycles [2].

Adriamycin and ifosfamide each have high activity when used alone [8]. In a first group of 14 patients in our ongoing study not only is the remission rate encouraging, but also the toxicity, when the drugs are given over 5 days, is encouragingly low. This combination may prove to combine the highest efficacy with the lowest toxicity and deserves more study.

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