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High-dose *cis*-platinum combination chemotherapy in advanced nonseminomatous malignant germ cell tumours with emphasis on nephrotoxicity*

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Summary. High-dose *cis*-platinum treatment (180 mg/m^2 per cycle) in combination with VP16 and bleomycin was given to 14 patients with highly advanced nonseminomatous malignant germ cell tumours (total: 31 cycles). *Cis*-platinum was administered in infusions of 0.9% NaCl given daily for 3 days with 3-week intervals. An intensive hydration regimen (7 l NaCl/day) provided a urinary output of at least 1000 ml/4 h. The response and side effects were evaluated. Ultimately 11 of 12 patients evaluable for treatment effect were rendered tumour-free and are alive with NED. All 14 patients were evaluable for toxicity; 2 developed life-threatening lung edema during the initial prehydration period and did not continue the high-dose *cis*-platinum schedule. After one to four cycles of high-dose *cis*-platinum treatment the ^{131}I-Hippuran clearance was reduced by 28%. Decreased kidney function evaluated by ^{131}I-Hippuran clearance was the reason for discontinuation of treatment in 5 patients. Patients with ureteric obstruction represented a high-risk group for reduction of kidney function. High-dose *cis*-platinum therapy is an intensive treatment demanding a high level of investment of resources, which has promising response rates in patients with highly advanced malignant germ cell tumours. Short-term clinically significant reduction of the kidney function can be avoided by intensive hydration of the patient.

Introduction

During recent years *cis*-platinum-based combination chemotherapy (with bleomycin/vinblastine or bleomycin/VP16) has become the treatment of choice in nonseminomatous malignant germ cell tumours, with an 85%–90% 3-years survival rate. However, for patients in advanced stages (≥ IIC) [7], with high levels of AFP, HCG [3], the survival rate is only about 50% when 'conventional' *cis*-platinum doses (100 mg/m^2 per cycle) are used. Patients with extragonadal malignant germ cell tumours are a high-risk group [2] for whom Ozols et al. [5] proposed a socalled high-dose *cis*-platinum treatment with 200 mg/m^2 *cis*-platinum in each course in combination with VP16, vinblastine and bleomycin. According to these authors, when *cis*-platinum in such high doses was given in a 3% NaCl infusion severe nephrotoxicity was avoided [6]. However, it has been shown in animal studies that the efficacy of high-dose *cis*-platinum may be reduced by the simultaneous application of 3% NaCl [1]. A prospective study was therefore initiated, in which patients with advanced malignant germ cell tumour were treated by high doses of *cis*-platinum using normal saline infusion. The intention was to evaluate the response to and the side effects, especially nephrotoxicity, of this regimen.

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Patients

Fourteen previously untreated patients with measurable disease were included in the study (age: mean 26.5 years; range 17–54 years). All but one patient had histologically documented malignant germ cell tumours. The other patient (no. 12, in Table 1), had a fine-needle aspirate from a large retroperitoneal mass and open biopsies from both testes performed, but these showed no tumour. However, the serum level of HCG was 774080 units/l, and he was therefore considered to be suffering from a malignant germ cell tumour. Nine patients had testicular tumours with retroperitoneal metastases larger than 10 cm, and seven of these also had lung metastases. Five patients had extragonadal germ cell tumours, four of them with advanced retroperitoneal tumours while one had large mediastinal tumours and multiple lung metastases. All patients had pathologic levels of AFP, HCG or both before therapy (Table 1). Seven of the patients had unilateral hydronephrosis owing to their large retroperitoneal tumours before the start of chemotherapy.

Treatment. The initial treatment of advanced malignant germ cell tumours (≥ stage IIb) at our hospital consists in four chemotherapy cycles, based on a modified Einhorn regimen (CVB: *cis*-platinum, Velbe, bleomycin) [3]. Chemotherapy is followed by reductive surgery if it is possible.

In the present series the intention was to substitute at least three of these courses with a high-dose *cis*-platinum regimen (see below) if no serious side effects were observed. The high-dose *cis*-platinum treatment was given daily for 3 days with 3-week intervals, as follows:

0.00 to 12.00 h: Prehydration with 3000 ml 0.9% NaCl containing 60 mmol KCl and 10 mmol MgCl

Table 1. Patient's characteristics and results

Patient	Clinical stage	AFP µg/l	HCG units/l	No of high-dose courses	Reason for change of therapy	Histology by retroperitoneal surgery	Months/status
1	$4CL_1$	276	<5	3		Necrosis	13/NED
2	2C	672	22900	1	Septicaemia ↓ ERPF	Mature teratoma	6/NED
3	$4CL_3H$	1835	12000	3		Malignant tumour	9/death
4	$2CL_3$	131	99400	2	Asthenia	Mature teratoma	9/NED
5	$4CL_2$	1760	4690	3		Necrosis	9/NED
6	$4CL_1$	4120	568	3	↓ ERPF	Mature teratoma	11/NED
7	2C	980	313	2	↓ ERPF	Necrosis	11/NED
8	$4CL_1$	672	3878	4		Mature teratoma	5/NED
9	$4CL_3$[a]	16	113750	2	↓ ERPF	Necrosis	8/NED
10	2C[a]	221	<5	3	↓ Blood counts	Mature teratoma	1/NED
11	2C[a]	<5	126	2	Asthenia, ototoxicity	Necrosis	2/NED
12	$4CL_3$[a]	<5	774080	3	↓ ERPF, ↓ blood counts	Necrosis	8/NED
13	$4CL_3$[a]	<5	288000	<1			
14	$4L_3$[b]	<5	181220	<1			

[a] Extragonadal
[b] Abdominal status unknown

12.00 to 13.00 h: 20 mg furosemide IV (bolus); *cis*-platinum 60 mg/m^2 in 500 ml 0.9% NaCl (30 min)

Vepesid 120 mg/m^2 in 500 ml 0.9% NaCl (30 min)

13.00 to 24.00 h: Hydration with 3000 ml 0.9% NaCl containing 60 mmol KCl.

The total amount of fluid was 7000 ml 0.9% NaCl. The output of urine per 4 h was recorded and furosemide was given if production of urine was less than 1000 ml per 4 hour. Bleomycin 30 mg was given IV on days 1, 5, and 15.

Eleven patients underwent retroperitoneal surgery after chemotherapy. In one of them (patient no. 5 in Table 1) thoracotomy was also performed, with resection of a residual lung density. One patient (no. 11 in Table 1) was not operated upon because of severe bleomycin-induced lung fibrosis. In this patient, a biopsy from the duodenum was the only investigation performed (a pretreatment biopsy from the same site had shown malignant germ cell tumour).

The follow-up time from discontinuation of chemotherapy was 1–13 months (median: 8.5 months).

Evaluation of tumour response. All patients who received at least one complete high-dose *cis*-platinum cycle were considered to be evaluable (12 patients). The response was judged on the basis of the histological findings in the resected retroperitoneal mass (11 patients) and on computer tomography-based measurements of the retroperitoneal tumour combined with biopsy (one inoperable patient: no. 11 in Table 1).

"Complete response" was recorded when totally necrotic tumour or mature teratoma was found in a completely resected specimen. Tumour shrinkage of more than 50% (WHO) combined with a tumour-negative biopsy indicated a "partial response" in inoperable patients. "No response" was recorded when vital malignant tumour cells were revealed in the post-chemotherapy histology.

Side effects were evaluated with reference to the following aspects:

Renal function was evaluated by determination of *S*-creatinine, creatinine clearance and ^{131}I-Hippuran clearance prior to each cycle and 3 weeks after the last course.

Creatinine clearance was calculated in accordance with the formula:

$$\text{Creatinine clearance} = \frac{(140 - \text{age})\ 2.12 \times \text{weight} \times S}{\text{Serum creatinine} \times \text{body surface}},$$

where S = 1 for men and S = 0.85 for women.

The ^{131}I-Hippuran clearance was measured according to a method developed by Pixberg [8] as a simplification of the Oberhausen method [4].

The values for ^{131}I-Hippuran clearance are given as percentages of the normal mean related to the age, sex, and body weight of the patients.

High-dose *cis*-platinum treatment was discontinued if a significant decrease in renal function was observed. This implied any demonstration of (a) a ^{131}I-Hippuran clearance $\leq 50\%$ and/or (b) a decrease in ^{131}I-Hippuran clearance by $\geq 20\%$ of the normal mean from one cycle to the next.

Blood count. Hemoglobin, leucocytes and platelets were determined prior to each cycle, twice weekly during the treatment-free interval and 3 weeks after the last cycle. Treatment was postponed until recovery if platelets were $\leq 100 \times 10^9$/l and leucocytes were $\leq 3 \times 10^9$/l on day 22.

General condition. The performance status (WHO) and body weight were assessed prior to each treatment and 3 weeks after primary chemotherapy. Auditory and neurological function was judged clinically.

Results

Treatment

Of the 14 patients, 2 did not complete the first cycle. Both had extensive lung metastases and developed severe lung oedema during the prehydration NaCl infusion (lethal in one patient). A total of 31 completed cycles of high-dose *cis*-platinum were administered in the remaining 12 patients: 1 patient received 4 cycles; 6 patients, 3 cycles; 4 patients, 2 cycles; and 1 patient only 1 cycle (Table 1).

Response

The high-dose *cis*-platinum combination chemotherapy was effective in 11 of the 12 patients (10 CR, 1 PR). They are alive with no disease activity, though one of them had to be re-treated with high-dose cisplatinum due to increasing HCG after surgery (patient 4). Viable malignant tumour was found in 1 of the 12 evaluable patients (no. 3 in Table 1). He subsequently developed liver metastases in spite of repeated high-dose *cis*-platinum treatment and died 9 months after the primary therapy.

Side-effects

Renal function. The renal toxicity is illustrated in Fig. 1. After discontinuation of high-dose cisplatinum treatment the mean decrease of ^{131}I-Hippuran clearance was 28% (range 0–55%) of the initial value. In 5 of the 7 patients with hydronephrosis high-dose *cis*-platinum treatment had to be discontinued before the three scheduled cycles were completed, owing to a decrease in renal function; 3 of these 5 patients had a normal value (>70%) before the start of therapy. None of the remaining 5 patients without ureteric obstruction had to stop the planned high-dose *cis*-platinum treatment. All of them had initial ^{131}I-Hippuran values above 70%.

The median value of creatinine and creatinine clearance changes are illustrated in Fig. 1. There was no tendency to increasing serum creatinine or decreasing creatinine clearance. One single serum creatinine value fell outside the normal range after the first high-dose *cis*-platinum cycle (142 µmol/l). In this patient a marginally raised serum creatinine was found even at the start of treatment (138 µmol/l). He had a unilateral hydronephrosis, with decreased renal function on that side because of the tumour mass. High-dose cis-platinum treatment was discontinued after one cycle in this patient.

Myelosuppression

The hematological toxicity is illustrated in Figs. 2 and 3. The median leucocyte count before each cycle tended to decrease slightly with increasing number of cycles, whereas the corresponding platelet count remained almost unchanged from one cycle to the next. The median nadir counts of leucocytes and platelets were registered on days 14 and 15, respectively. In patient no. 10 prolonged leucopenia ($<3\times10^9$/l) and thrombocytopenia ($<100\times10^9$/l) caused discontinuation of the high-dose *cis*-platinum treatment after three cycles, and in patient no. 12 the decreased blood counts and ^{131}I-Hippuran clearance were the reason for changing the chemotherapy.

The median nadir counts of platelets were less than 40×10^9/l. The median nadir counts of leucocytes were $1.3-1.7\times10^9$/l.

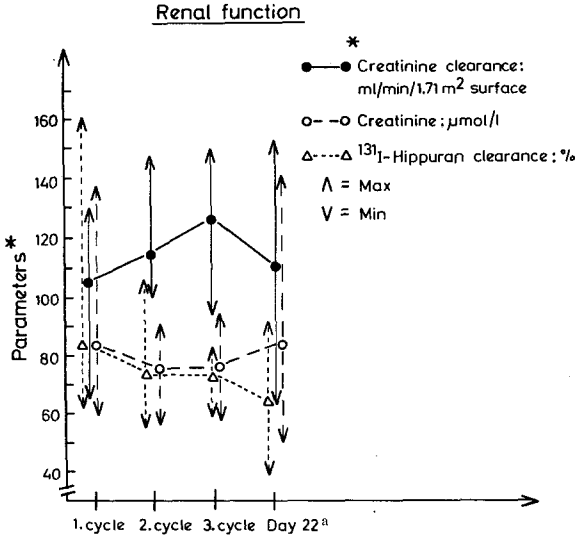

Fig. 1. Renal function, during treatment with high-dose cis-platinum regimen
[a] Day 22: After the patients last cycle.

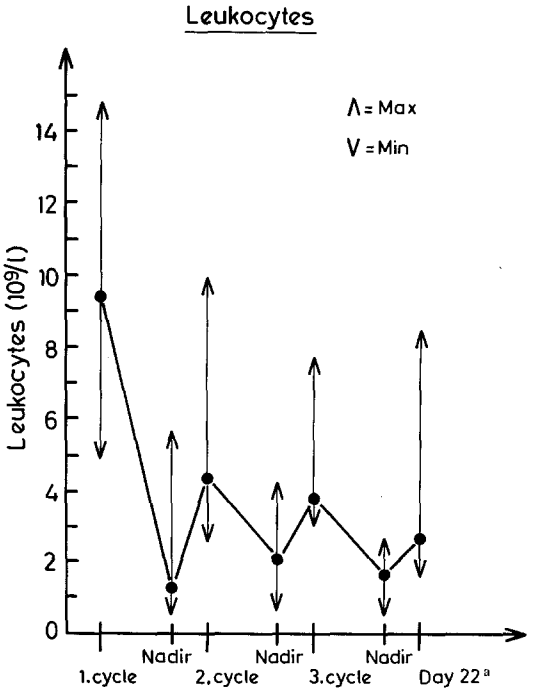

Fig. 2. Leucocyte count, during treatment with high-dose cis-platinum regimen
[a] Day 22: After the patients last cycle.

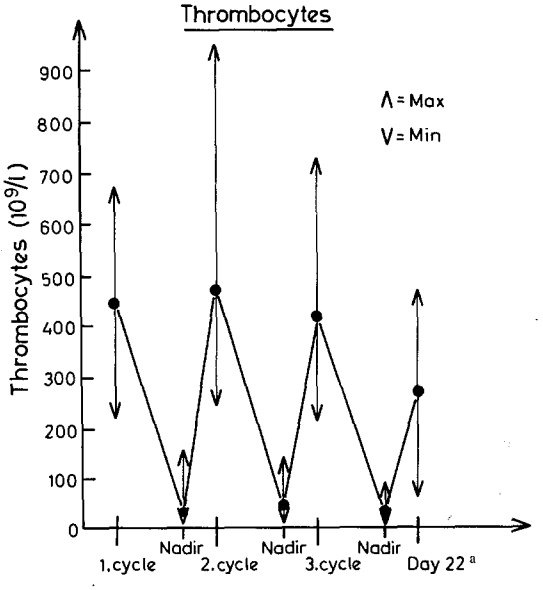

Fig. 3. Thrombocyte count, during treatment with high-dose cis-platinum regimen
[a] Day 22: After the patients last cycle.

General condition. The nausea and vomiting experienced by the patients during treatment was more pronounced than that seen with the regular CVB regimen, but could be controlled by dexamethasone and metoclopramide. The median loss of weight was 4.5 kg (range 0–12 kg). In eight patients the performance status changed from 0 to 1 during the chemotherapy period. In three patients with an initial performance status of 3 the general condition improved after one cycle (WHO status 1).

Slight hearing loss was recorded in three patients (patients 7, 10 and 11 in Table 1). No audiometry was performed. Four patients (patients 1, 6, 8 and 4) developed a slight degree of peripheral polyneuropathy.

After 13 of 31 cycles, admission to hospital was necessary in eight patients owing to complications (myelosuppression, septicaemia, subileus).

Discussion

Ozols et al. suggest that the "apparent protective effect of the hypertonic saline may relate to the equilibrium between the parent diaminnedichloro form of platinum and the aquated form", though these authors also express some doubts about the renal protection [5]. Our results indicate that the use of 3% saline is unnecessary for the avoidance of severe reduction of the kidney function if intensive hydration is applied. In addition, animal studies [1] have shown that 3% NaCl infusion may reduce the cytotoxicity of high-dose *cis*-platinum, whereas a high cytoreductive activity was demonstrated with normal saline infusions.

Furthermore, our findings indicate that measurements of serum creatinine and evaluation of creatinine clearance are too insensitive to reveal small alterations of renal function. The above parameters remained unchanged in all our patients, though the more sensitive ^{131}I-Hippuran clearance test revealed a general reduction in renal function by 28%. We do not know the clinical significance of this reduction in renal function. It may be transitory and therefore clinically irrelevant for these patients with very advanced testicular cancer, who have a poor prognosis if not treated aggressively. The long-term clinical significance of this reduction of kidney function also remains unknown, especially against the background of the unchanged serum creatinine values. Possibly one should continue high-dose *cis*-platinum treatment irrespective of a decreased ^{131}I-Hippuran clearance as long as the serum creatinine remains normal. In patients with hydronephrosis resulting from ureteric stenosis temporary nephrostomy should be considered to avoid serious interference with renal function during high-dose *cis*-platinum treatment.

High-dose *cis*-platinum therapy is an intensive medical treatment demanding as great an investment of resources as many major surgical procedures. During the initial treatment the risk of overhydration is significant and can be life-threatening in patients with extensive lung metastases. Severe myelosuppression has to be expected after treatment, necessitating admission to hospital in the majority of patients. On the other hand, the subjective toxicity seems to be acceptable in these patients, as long as no more than three to four cycles of high-dose *cis*-platinum treatment are given. Within the short observation period, the curative effect of high-dose *cis*-platinum treatment seems to be promising in patients with malignant germ cell tumours and large tumour burden: 11 of 12 patients were rendered tumour-free. These results appear to be superior to those obtained by "conventional CVB-treatment" in comparable patients at our institution (only 12 of 21 were rendered tumour-free by CVB; unpublished results). How far the increased dose of *cis*-platinum is responsible for the improved results, or whether the introduction of Vepesid has had a significant influence, cannot be decided [9]. Only a randomized study with Vepesid given in both arms can demonstrate the necessity of using high-dose *cis*-platinum in high-risk patients with malignant germ cell tumours.

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