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A Phase I/II Study of a Stepwise Dose-escalated Regimen of Cisplatin, Etoposide and Ifosfamide plus Granulocyte–Macrophage Colony-stimulating Factor (GM-CSF) in Patients with Advanced Germ Cell Tumours

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In order to improve the survival of patients with metastatic advanced disease germ cell tumours (according to Indiana University classification), 77 patients were treated by a stepwise dose-escalated combination regimen of platinum (P), etoposide (E) and ifosfamide (I) (PEI) followed by application of granulocyte–macrophage colony-stimulating factor (GM-CSF) (10 μg/kg subcutaneously per day at levels 2 and 3) starting the first day after chemotherapy for 10 consecutive days. The maximally tolerated dose was reached at the third dose level with P 30 mg/m², E 200 mg/m² and I 1.6 g/m², all given for 5 days, once every 21 days, for a total of four cycles. Sixty-seven per cent of patients had three or more metastatic sites. Twenty-two per cent of patients had extragonadal primary tumours. 49 (65%) patients achieved complete remission, and 9 additional patients (12%) achieved marker normalisation with unresectable residual disease. After a median follow-up of 27 months, the overall survival is 80%, with 67% of patients remaining free from progression. The dose-limiting toxicities were WHO grades 3/4 mucositis/enteritis in 33% of patients and prolonged thrombocytopenia < 20.000/μl (> 10 days). Adverse reactions to GM-CSF occurred in 13% of patients. The use of a single haematopoietic growth factor allowed only a moderate increase in dose intensity (factor 1.37). Peripheral blood stem cells will be additionally incorporated into the treatment protocol in order to deliver multiple cycles of an upfront dose-intensified PEI regimen in patients with "poor risk" germ cell tumours with less toxicity.

Key words: advanced germ cell tumours, dose intensity, platinum/etoposide/ifosfamide, GM-CSF
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INTRODUCTION

WITH THE introduction of effective combination chemotherapy, testicular cancer has become a model for a highly curable malignant disease [1]. About 80% of all patients with metastatic testicular cancer will achieve a durable complete remission (CR) [2]. The application of prognostic factors enables one group of patients with an exceptionally high chance of cure to be distinguished from another subset of patients, designated "poor risk", in whom only a complete response rate of 40–70% can be achieved with standard chemotherapy regimens [3]. Different strategies have been investigated to improve the unsatisfactory results in these poor-risk patients, including the incorporation of additional agents to the three drug regimens, the rapid alternation of drug regimens or the increase of dose intensity [4–8].

A dose–response relationship was shown for patients with germ cell tumours treated with cisplatin doses between 60 and 120 mg/m² and this prompted the investigation of cisplatin administered at 200 mg/m² per cycle (double-dose cisplatin) [4]. A benefit for double-dose cisplatin in combination with etoposide, bleomycin and vinblastin over standard PEB (platin/etoposide/bleomycin) was suggested in a randomised trial for patients with poor-risk germ cell tumours performed at the National Cancer Institute (NCI) of the U.S.A. [5]. However, a

phase II trial incorporating double-dose cisplatin and a randomised prospective trial of double-dose cisplatin, etoposide, bleomycin (PEB) versus standard PEB demonstrated that doubling the dose of cisplatin increased the morbidity without improving the efficacy of treatment [6, 7]. Therefore, the optimal cumulative dose of cisplatin per treatment cycle is estimated to be between 100 and 150 mg/m^2.

Besides cisplatin, etoposide and ifosfamide are the two most active single agents for the treatment of testicular cancer. In pretreated patients, this three-drug combination has exhibited high activity, indicating a clinically relevant synergism [9, 10]. For both agents, clinical data suggest a dose–response relationship. Elias achieved nine objective responses in 27 patients, who were refractory to standard dose ifosfamide, by the use of high-dose ifosfamide up to 18 g/m^2 [11]. Etoposide has demonstrated single-agent activity in previously treated patients with testicular cancer [12]. Very high doses of etoposide (2400 mg/m^2) followed by autologous bone marrow rescue have produced responses in patients refractory to standard dose etoposide [13]. The main toxicity associated with escalated doses of ifosfamide and etoposide appears to be myelosuppression. However, the availability of granulocyte–macrophage colony-stimulating factor (GM-CSF) has made it possible to ameliorate the chemotherapy-induced granulocytopenia. Therefore, the concomitant application of GM-CSF might allow a dose intensification of several antineoplastic agents [14].

Following the rationale outlined above, we have conducted a phase I/II study of stepwise dose escalation of etoposide and ifosfamide combined with a fixed dose of cisplatinum (PEI regimen) followed by subcutaneously (s.c.) applied GM-CSF. The aims of the study were to establish the maximally tolerated dose level, and to gather data on the therapeutic efficacy of this escalated PEI regimen in first line therapy of patients with advanced germ cell cancer.

PATIENTS AND METHODS

Eligibility criteria

Patients with advanced, histologically confirmed germ cell cancer were eligible. Advanced disease was defined according to the criteria of the Indiana University [15], which are palpable abdominal disease (> 10 cm) plus pulmonary metastases (any size) and/or supradiaphragmatic lymph node metastases; advanced pulmonary metastases defined as mediastinal mass > 50% of the intrathoracic diameter, or more than 10 lung metastases per lung field, or multiple metastases > 3 cm; visceral metastases (bone, liver, brain, etc.); primary mediastinal germ cell tumour.

A pathology review of all tumours was carried out in order to confirm the diagnosis and to classify all histological specimens according to the British Tumour Panel [16]. Further eligibility criteria included a normal bone marrow function [defined as white blood cells (WBC) > 3000/μl and thrombocytes > 100 000/μl], normal liver (bilirubin < 2× upper limit, unless caused by liver involvement with tumour) and renal function (creatinine clearance > 70 ml/min), no co-existing clinically relevant cardiovascular disease, no prior chemotherapy and informed consent. Poor performance status was not considered as a reason for exclusion from the study.

Treatment protocol

The trial consisted of three dose levels, starting with an intensified standard regimen of cisplatinum 25 mg/m^2, etoposide 120–150 mg/m^2 and ifosfamide 1.2 g/m^2 each given from days 1 to 5 every 3 weeks at dose level 1. Patients at this dose level did not receive GM-CSF. The next steps of the escalation protocol called dose levels 2 and 3, involving concomitant application of GM-CSF (Essex Pharma, Munich, Germany), are given in Table 1.

All antineoplastic drugs were applied as 1-h infusions with appropriate supportive measures including the use of the uroprotective agent sodium mercaptoethanesulfonate (Mesna) as a short infusion before and 3 and 6 h after ifosfamide, intravenous (i.v.) hyperhydration of 3 l/m^2 of 5% glucose and isotonic saline as a 24-h continuous infusion and prophylactic anti-emetics, mostly ondansetrone (32 mg i.v.) and dexamethasone (20 mg i.v.). Starting with dose level 2, GM-CSF was administered for 10 consecutive days (days 6 to 15), starting the first day after chemotherapy, s.c., at a dose of 10 μg/kg per day. In dose level 3, GM-CSF was reduced to 5 μg/kg × day in the last 22 patients, since this dose might be associated with the same clinical efficacy but with less toxicity. Application of GM-CSF was prolonged for an additional 3 days if the WBC count had not reached 2000/μl on day 15. The chemotherapy cycles were repeated every 3 weeks if leukocytes were > 3000/μl and thrombocytes > 100 000/μl at that time. Four cycles per patient were scheduled. For patients in dose level 3, who had liver metastases involving more than 50% of the liver or pulmonary metastases with significant clinical dyspnea, the doses of all three drugs were reduced to 50% of the planned escalated dose for the first cycle. When at least 15 patients had been entered at a given dose level and toxicity was considered tolerable, the study moved to

Table 1. Dose escalation scheme of PEI therapy

	Dose level		
	1	2	3
Cisplatin (mg/m^2) days 1–5	25	30	30
Etoposide (mg/m^2) days 1–5	120	150	200
Ifosfamide (mg/m^2) days 1–5	1200	1600	1600
GM-CSF (μg/kg) days 6–15	—	10	10/5

Cycles were repeated on day 22 for a total of four cycles. GM-CSF is given s.c. at each cycle in levels 2 and 3.

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the next escalation step. No dose escalation was performed within 1 patient.

Study parameters

The initial assessment of the patients included history, physical examination, whole and differential blood counts, blood chemistry, tumour markers, creatinine clearance, ultrasound of the abdomen, chest X-ray, computed tomography (CT) scans of the abdomen, lung and brain, and bone scans. Prior to each treatment cycle, all evaluable and measurable sites of disease were assessed. During treatment, blood counts were performed at least every second day, and differential blood counts and blood chemistry twice weekly. Tumour markers, creatinine clearance and assessment of toxicity were conducted prior to each cycle.

Response was assessed using standard criteria, with the exception of the term "marker negative partial remission" (PRm-), which was used for all patients with residual tumours and normalisation of serum tumour markers. Toxicity was graded according to the modified WHO scale.

In patients achieving a marker negative status, surgical removal of all residual disease was attempted. Patients with complete surgical resection of viable tumour were defined as "no evidence of disease" (NED).

Follow-up consisted of the assessment of clinical status, by CT scans and ultrasound examinations, and the determination of serum tumour markers. Intervals were every 2–3 months throughout the first year, every 3–4 months during the second year and every 6 months thereafter. Patients suffering from relapse or with incomplete response were treated according to the decision of the individual physician. However, patients with only slight elevations of markers after dose-escalated PEI therapy received POMB-ACE (platinum, vincristine, methotrexate, bleomycin followed by actinomycin D, cyclophosphamide and etoposide) [8]. Attempts were made to enter most patients with relapse on a salvage protocol with high-dose carboplatinum/etoposide/ifosfamide followed by autologous bone marrow support.

In addition to the Indiana University classification for advanced disease, the statistical model of Bosl *et al.*, developed at the Memorial Sloan–Kettering Cancer Center (MSKCC) [17], was used to calculate the probability of achieving a CR/NED status for each patient. This calculation is based on an equation which includes the serum lactate dehydrogenase (LDH) and β-human chorionic gonadotrophin (β-HCG) levels, and the number of metastatic sites (totmet), ranging from 0 to 2. The mean probability of CR/NED for all patients at each separate dose level was compared to the achieved results.

The durations of response and survival were measured from the end of therapy. Survival was calculated according to Kaplan and Meier [18] for the whole study group, and separately for patients treated at the three different dose levels. Patients with early death due to therapy or tumour were included in the calculation of survival. The differences in response rate were analysed for statistical significance using the χ^2 test and survival data were analysed using the log rank test [19].

RESULTS

Patients

77 patients were entered into the trial: 18 patients were treated at dose level 1, 15 patients at dose level 2, and 44 patients at dose level 3. Of the 18 patients entered at level 1, 2 were not evaluable because of non-advanced disease in 1 case and the finding of sarcoma of the testis on review pathology in the other. The patients' characteristics are summarised in Table 2. Most patients had gonadal primaries (77%); however, the number of patients with primary extragonadal mediastinal germ cell tumours increased from 6% in level 1 to 11% in level 3. The histological distribution was fairly common for a given group of germ cell tumour patients. Only at level 1, 2 patients with advanced metastatic seminoma were included. The percentages of patients with three or more sites of metastatic disease were 50% in level 1, 53% in level 2 and 77% in level 3 ($P = 0.05$). The percentages of patients with metastatic involvement of the liver were 19% in level 1, 27% in level 2 and 41% in level 3 ($P = 0.06$); overall, 33% of the study population showed metastatic disease in the liver.

Table 2. Characteristics of patients entered on dose levels 1, 2 and 3 including the number of metastatic sites and specific locations of disease

	Dose level 1	2	3	All
Number of patients entered	18	15	44	77 —
Not evaluable	2	—	—	
Sarcoma histology	1	—	—	
Non-advanced disease	1	—	—	
Number of patients evaluable	16	15	44	75 —
Primary tumour				
Gonadal	13 (81%)	12 (80%)	33 (75%)	58 (77%)
Retroperitoneal	2 (13%)	2 (13%)	6 (14%)	10 (13%)
Mediastinal	1 (6%)	1 (7%)	5 (11%)	7 (9%)
Histology				
Seminoma	2 (13%)	—	—	2 (3%)
MTU	4 (25%)	4 (27%)	11 (25%)	19 (25%)
MTI	6 (38%)	7 (47%)	20 (45%)	33 (44%)
MTT	4 (25%)	4 (27%)	13 (30%)	21 (28%)
No. of metastatic sites				
1–2	8 (50%)	7 (47%)	10 (23%)	25 (33%)
⩾ 3	8 (50%)	8 (53%)	34 (77%)	50 (67%)
Specific localisations				
Liver	3 (19%)	4 (27%)	18 (41%)	25 (33%)
Bone	1 (6%)	2 (13%)	3 (7%)	6 (8%)
CNS	3 (19%)	2 (13%)	3 (7%)	8 (11%)
Calculated chance of achieving CR/NED*	57%	44%	33%	—
Median follow-up (months)	39	30	20	27

*According to Bosl [17], based on total number of metastatic sites, LDH and β-HCG. CNS, central nervous system; MTU, malignant teratoma undifferentiated; MTI, malignant teratoma intermediate; MTT, malignant teratoma trophoblastic.

The median follow-up for the whole study population was 27 months, with 39 months (range 28–48), 30 months (range 24–36) and 20 months (range 6–26) at dose levels 1–3, respectively. 8 patients at level 3 had been followed for less than 1 year.

Response, follow-up and survival

The results of treatment are summarised in Table 3. 11 of 16 patients (69%) reached CR/NED at level 1, and 10/15 (67%) patients and 28/44 (64%) patients at levels 2 and 3, respectively. 38 of 49 patients (78%) required additional surgery of residual

Table 3. Response to treatment and follow-up for patients treated at dose levels 1–3

	Dose level 1 (16 patients)	2 (15 patients)	3 (44 patients)	All (75 patients)
CR/NED	11 (69%)	10 (67%)	28 (64%)	49 (65%)
Chemotherapy alone	1	2	8	11
Resection of necrosis	7	6	16	29
Resection of teratoma	1	1	2	4
Resection of carcinoma	2	1	2	5
PR marker normalisation	2 (13%)	1 (7%)	6 (14%)	9 (12%)
PR-positive markers or progression	2 (13%)	3 (20%)	6 (14%)	11 (15%)
Toxic death	1 (6%)	1 (7%)	4 (9%)	6 (8%)
Relapse from CR/NED	2 (18%)	0 (0%)	0 (0%)	2 (4%)
Progression from PRm−	2 (100%)	1 (100%)	3 (50%)	6 (67%)
Continuously free from progression	9 (56%)	10 (67%)	31 (70%)	50 (67%)
Currently CR/NED or PR with normal markers	10 (63%)	12 (80%)	35 (80%)	57 (76%)

tumours to achieve CR/NED. The histology of the resected specimen showed necrosis in 29 patients (76%), mature teratoma in 4 (11%) and viable carcinoma in 5 patients (13%). These 5 patients received no additional chemotherapy.

9 patients (12%) have reached a marker normalisation with unresectable residual disease. 11 patients (15%) achieved only remissions with positive markers (8 patients), or were progressive directly after the escalated PEI therapy (3 patients). Of these patients, 2 were subsequently rendered marker-negative by POMB-ACE therapy and 3 by high-dose therapy with carboplatin/etoposide/ifosfamide followed by autologous bone marrow support. However, only minimal marker-positive disease was present in these patients at the time of salvage therapy. Compared to the mean calculated chance of achieving a CR/NED status, according to Bosl [17] (MSKCC classification), the CR/NED rates for patients were 69% compared to 57% calculated at dose level 1 ($P = 0.07$); 67% compared to 44% calculated for patients at level 2 ($P < 0.05$) and 64% compared to 33% calculated at level 3 ($P < 0.02$).

2 patients have relapsed from CR/NED and 6 patients have progressed from PRm− after a median follow-up of 27 months. 2 of these patients have been subsequently salvaged, 5 have died from their disease and 1 is currently under treatment. After a median follow-up of more than 2 years, the overall survival is 80%, and 50 patients (67%) have remained free from progression.

The Kaplan–Meier plots for overall and event-free survival for all patients (Figs 1, 2), and according to dose levels (Figs 3, 4) were calculated. Patients dying from therapy-related toxicity were included for the calculation of response rates as therapy failures.

Toxicity

The non-haematological toxicity at dose level 1 was not different from that expected with standard dose therapy. With

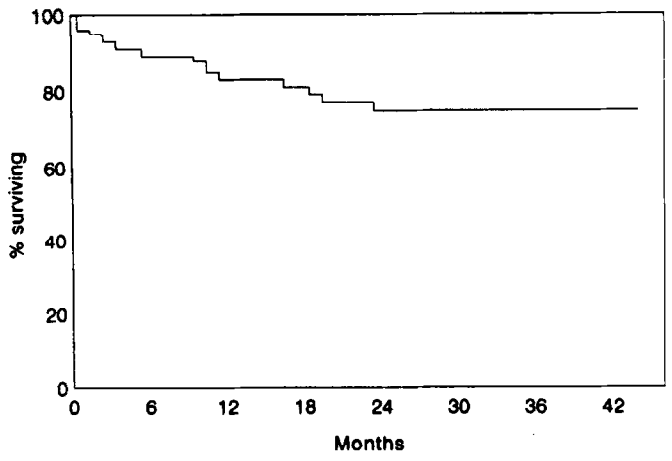

Fig. 1. Overall survival of patients ($n = 75$) treated by dose-intensified PEI chemotherapy followed by GM-CSF.

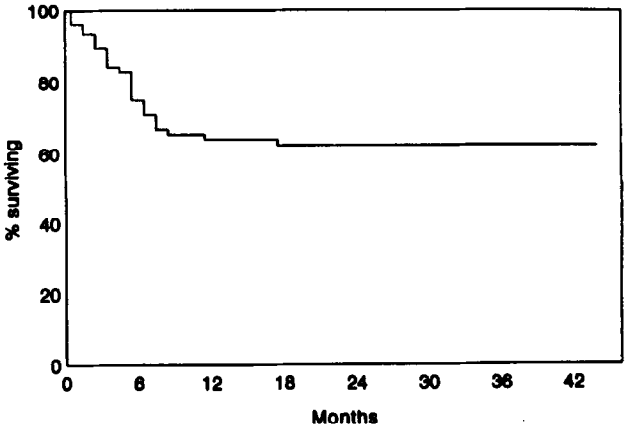

Fig. 2. Event-free survival of patients ($n = 75$) treated by dose-intensified PEI chemotherapy.

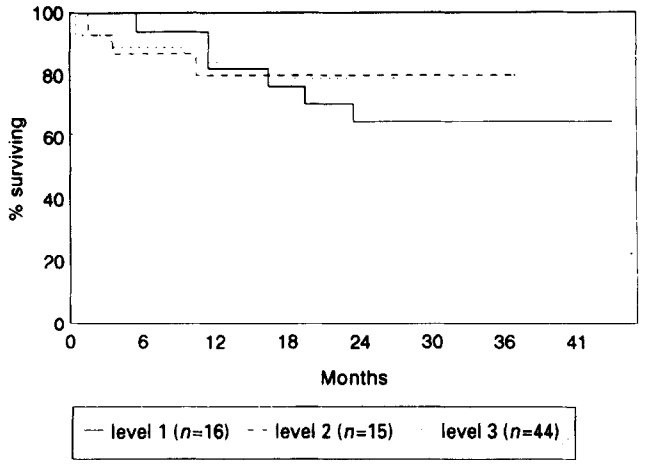

Fig. 3. Overall survival of patients treated at the dose levels 1, 2 and 3.

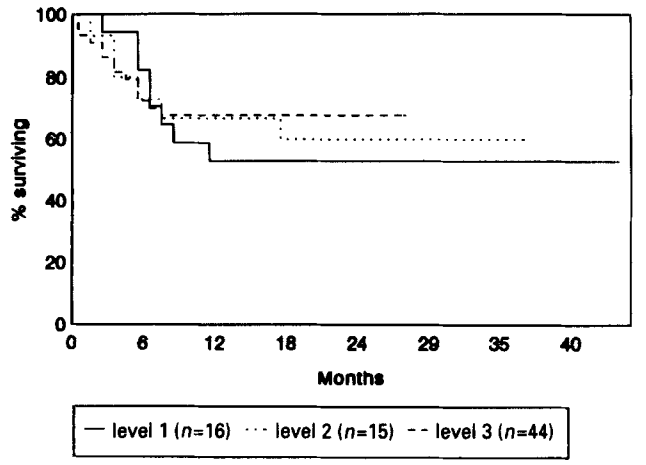

Fig. 4. Event-free survival of patients treated at the dose levels 1, 2 and 3.

Table 4. Non-haematological toxicity (WHO grades 3/4) of escalated PEI chemotherapy for dose levels 1, 2 and 3, expressed as the worst toxicity per patient

	Dose level 1		2		3		All	
	WHO grade 3	4	3	4	3	4	3	4
Nausea/ vomiting	50%	6%	47%	7%	36%	10%	41%	8%
Mucositis	11%	—	20%	13%	32%	2%	25%	4%
Renal toxicity	—	—	—	7%	7%	—	1%	1%
Diarrhoea	6%	—	7%	—	34%	—	23%	—
Liver toxicity	6%	—	7%	—	2%	—	4%	—
Neurotoxicity	—	—	—	—	4%	2%	3%	1%

the escalated doses of etoposide and ifosfamide used at levels 2 and 3, an increase of WHO grades 3 and 4 mucositis was noted with 33% at level 2 and 34% at level 3. Renal toxicity was moderate; only 1 patient who suffered from an aspergillus pneumonia and subsequently died required temporary haemodialysis. No significant liver toxicity was seen. Nausea and vomiting were noted in approximately 50% of patients at all three dose levels despite prophylactic anti-emetic therapy. Neurological toxicity (WHO grades 3/4) occurred in 3 patients, all treated at dose level 3. The neurological toxicity was completely reversible in 2 patients while the third patient still suffers from weakness of his lower extremity muscles. A summary of the non-haematological toxicity is given in Table 4. The dose-limiting non-haematological toxicities were severe mucositis and/or diarrhoea at dose level 3.

The haematological toxicity is summarised in Table 5. The severity of leukocytopenia increased with each dose level, and from cycle 1 to cycle 4 within all three dose levels. The median number of days with leucocyte counts below 500/μl was 8 at dose level 3 with a median of 5 days in cycle 1 and 12 days in cycle 4.

Thrombocytopenia below 20000/μl was the dose-limiting

Table 5. Haematological toxicity, treatment delay and dose intensity of levels 1–3

	Dose level 1 cycles number 1 and 4	2 cycles number 1 and 4	3 cycles number 1 and 4
Number of days with leukocytes < 500/μl	5 4/7	6 4/9	8 5/12
Number of days with thrombocytes < 20000/μl	3 1/4	5 2/8	6 2/11
Platelet transfusions (% of cycles)	51%	78%	100%
Infections/fever (% of cycles)	42%	64%	70%
Median delay to next cycle (days)	2 0/4	3 0/6	5 0/6
Dose intensity (% of planned dosages)	94%	94%	82%
Dose intensity compared to standard PEI	1.12	1.24	1.37

For the duration of leukocytopenia and thrombocytopenia, the median number of days for all dose levels and for cycles 1 and 4 at each level are given.

haematological toxicity, with a median of 3 days at level 1 and 6 days at level 3. The duration of thrombocytopenia < 20000/μl after the fourth cycle increased from a median of 4 days at level 1 to 11 days at level 3. All patients treated at dose level 3 required platelet transfusions.

Infections and fever occurred in 42% of patients treated at dose level 1 and 70% treated at level 3.

The median length of a treatment cycle increased from 23 days at level 1 to 24 and 26 days at levels 2 and 3, respectively. Subsequently, the dose intensity dropped from 94% of the planned dose at level 1 to 82% at level 3. Compared to a standard dose PEI regimen the median dose intensity achieved was 1.12 for level 1, 1.24 for level 2 and 1.37 (planned 1.70) for level 3.

6 patients (8%) died during therapy. 3 patients (1 at level 1, 2 at level 3) died from septicaemia, 1 patient at level 2 from an aspergillus pneumonia, and 2 patients at level 3 died from bleeding complications: 1 patient with pulmonary haemorrhage due to massive tumour lysis during the first cycle of therapy, and 1 patient from intracerebral bleeding during a thrombocytopenic episode following the fourth chemotherapy cycle.

62 patients were treated with GM-CSF after chemotherapy. 40 patients received a dose of 10 μg/kg daily, 22 patients received 5 μg/kg (all at dose level 3). 5 patients had an anaphylactic-type reaction with bronchospasm, myalgia, erythema and fever shortly after the administration of GM-CSF. 2 patients developed fever without signs of infection directly after GM-CSF application. 1 patient showed a severe erythema localised to the site of injection. Overall, 8 patients (13%) had to discontinue GM-CSF. 3 patients were subsequently treated with G-CSF (Amgen, Munich, Germany), 3 received no further growth factors, and 1 patient was retreated with GM-CSF under the protection of corticosteroids. No differences in the frequency of side-effects were seen in patients receiving either 10 or 5 μg/kg of GM-CSF.

DISCUSSION

Although cisplatin-based chemotherapy is a highly effective treatment for patients with germ cell tumours, there remains a group of patients who are not cured by this therapy. Several attempts, including multivariate analysis of large groups of patients, have been carried out to define precisely which patients have a poor prognosis [17, 20, 21]. Patients treated at Indiana University are divided into three groups with minimal, moderate and advanced disease [15]. This classification relies on easily available parameters of tumour volume and the distribution of metastases. In a large randomised trial, patients with advanced disease receiving standard PEB treatment achieved a 73% CR/NED rate and 61% still remain free from progression after a follow-up of 2 years [7].

In order to improve the chances of cure in patients with advanced germ cell tumours, several concepts have been investigated. The inclusion of additional active drugs to standard regimes and the use of alternating regimens has been one line of investigation. A recent report about the use of the POMB/ACE regimen, initially suggested by Newlands in 1983 [22], has yielded a CR rate of 56% in patients with metastatic non-seminomatous germ cell tumours with large or very large volume disease [23]. The 5-year survival rate for this particular subgroup of patients was 67%. While there was no advantage for the whole group, this trial demonstrated that patients who received a higher relative dose intensity of etoposide had a significantly improved survival, suggesting that the dose intensity of this drug may be an important determinant for the outcome of metastatic germ cell tumours.

In a phase II study of 48 patients with advanced testicular cancer a CR rate of 71% was reached by a regimen alternating cisplatin, etoposide, bleomycin and vincristine with nadir-adapted ifosfamide [24]. Comparable results were achieved in another phase II trial using an alternating regimen of cisplatin, vincristine and bleomycin (BOP) and cisplatin, etoposide and ifosfamide (VIP) [25]. This new regimen is currently being compared to standard PEB therapy by the Medical Research Council and the EORTC. The other line of investigation pursues the intensification of the dose intensity of the most active drugs. Based on the demonstration of a dose–response relationship for cisplatin at doses between 75 and 120 mg/m^2 [4], and an improved activity of an intensified four-drug regimen over a standard three-drug regimen reported by Ozols *et al.* [5], further trials with increased dosages of cisplatinum in patients with advanced disease were initiated [6, 7]. In one phase II study with 72 patients employing escalated doses of cisplatin at 40 mg/m^2 and etoposide at 200 mg/m^2 daily for 5 days followed by standard-dose bleomycin, a CR rate of 75% was obtained. After a median follow-up of nearly 4 years, 67% of patients are without evidence of disease. However, the myelotoxicity was severe and 10% of patients died due to treatment-related toxicity [26].

The use of megadose treatment as induction therapy for poor-risk patients followed by autologous bone marrow support has taken this line of investigation further. The use of ultra-high-dose regimens appears to be better tolerated during induction therapy compared to treatment for relapsed disease [27]. Patients with an inappropriately slow decline of serum tumour markers after two cycles of standard induction therapy may profit from early megadose regimens [3]. However, the first randomised trial, in 114 patients with advanced germ cell tumours comparing four cycles of the NCI regimen [5] of platinum, etoposide, vinblastine and bleomycin with two cycles of the same induction regimen followed by megadose therapy with platinum/etoposide/cyclophosphamide plus autologous bone marrow support demonstrated no significant advantage for the megadose regimen [28]. We performed a stepwise escalation of the three-drug regimen cisplatin/etoposide/ifosfamide given together with GM-CSF, in order to ameliorate granulocytopenia and to establish the maximal tolerable dosage of this three-drug combination. Dose escalations were performed in three steps, including 18, 15 and 44 patients in levels 1, 2 and 3, respectively. The third dose level, using a cumulative dose of cisplatin 150 mg/m^2, etoposide 1000 mg/m^2 and ifosfamide 8 g/m^2 per cycle was considered as maximally tolerable. The major toxicities were prolonged thrombocytopenia, with 100% of patients requiring platelet transfusions and a median duration of thrombocytopenia (< 20000/μl) of 2–11 days, and severe mucositis which developed in about one third of patients. Even with the application of GM-CSF, granulocytopenia was still severe and myelosuppression increased with the number of treatment cycles applied. Though the study was not designed to evaluate the effects of GM-CSF, it was possible to compare the myelosuppression produced by the same dose of therapy in those patients who had GM-CSF discontinued because of adverse reactions to those patients who received the planned doses of GM-CSF. The time to leukocyte recovery to over 3000/μl was significantly longer (20–32 days) for courses without GM-CSF, compared to those with GM-CSF (17–24 days) ($P < 0.05$). No significant difference in myelotoxicity was seen between those 22 patients at dose level 3, who received a GM-CSF dose of 10 μg/kg per day,

compared to 22 patients receiving only 5 μg/kg per day. However, a tendency towards shorter duration of leukocytopenia and thrombocytopenia for patients receiving the higher dosage of GM-CSF was observed during cycles 3 and 4 of PEI chemotherapy. Adverse events to GM-CSF occurred in patients treated with both dosages of GM-CSF.

The non-haematological toxicity of dose levels 1 and 2 was not significantly different from that expected with the standard PEI regimen. Apart from severe nausea and vomiting and the mucositis observed at dose level 3, severe toxicities, including neurotoxicity or renal toxicity, have only been single events in this patient population. Although concerns have been raised by reports demonstrating an increased incidence of secondary leukaemia after high-dose etoposide treatment [29], no cases of secondary leukaemia or other neoplasms have been observed in our patients so far. However, a longer follow-up is necessary to exclude these adverse events.

This dose-escalated regimen achieved an overall favourable response rate (defined as CR/NED and remission with marker normalisation) of 77% and an overall survival of 80% after a median follow-up of 27 months. It must be kept in mind, that the study was not designed to demonstrate significant differences between the different dose levels used. However, the 2-year survival rate for patients at dose level 3 was 82% compared to only 63% for patients treated at level 1. This difference is even more surprising since patients at level 3 possessed much worse clinical characteristics than patients at level 1, e.g. expressed by the median calculated chance of achieving CR according to MSKCC criteria (57% for level 1 versus 33% for level 3).

Calculating the relative dose intensity of the three-drug regimen at each dose level, mean dose intensities of 1.12 at level 1, 1.24 at level 2 and 1.37 at level 3 were reached compared to a standard PEI regimen. It must, therefore, be questioned whether the use of a single haematopoietic growth factor following intensive chemotherapy may allow clinically meaningful dose escalations. Further supportive measures, such as the use of peripheral blood stem cells (PBSC), will be incorporated into the treatment protocol in order to allow the application of multiple cycles of upfront dose-intensified chemotherapy. If this approach will reduce the side-effects of the maximally tolerated dose level 3 or even allow a further increase in dose intensity with acceptable toxicity, the true value of an upfront dose-escalated regimen for the treatment of advanced testicular cancer should be evaluated in a prospective randomised study in comparison to standard-dose chemotherapy.

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