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Intensive Induction Chemotherapy for Poor Risk Non-seminomatous Germ Cell Tumours

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Abstract—*An increase in initial chemotherapy intensity was evaluated in 29 patients with high risk metastatic non-seminomatous germ cell tumours (NSGCT) of the testis, defined by the presence of multiple large lung metastases, liver, bone or brain metastases, or the combination of large abdominal mass with high serum concentration of the tumour markers alpha-foetoprotein (AFP) or beta subunit of human chorionic gonadotrophin (HCG) (AFP > 500 ku/l or HCG > 1000 iu/l). Four courses of bleomycin, vincristine and cisplatin (BOP) were given at 7 day intervals, followed by three courses of etoposide, cisplatin with or without bleomycin (BEP or EP) at 21 day intervals for a total of 13 weeks of chemotherapy. Twenty-three (85%) of 27 evaluable patients have remained continuously free from disease progression at a median of 24 months (range 14–38 months) from chemotherapy and the actuarial 2 year freedom from progression rate is 86% (95% CI = 73–99%). Three patients died from non-malignant causes, two of bleomycin pneumonitis and one from complications of cystic fibrosis. Thus cause specific overall survival in the total population of treated patients is 79%. With appropriate limitation of bleomycin dosage, this approach is well tolerated and results compare favourably with less intensive induction schedules based on initial 21–28 day cycles.*

INTRODUCTION

CHEMOTHERAPY is very successful in the management of metastatic NSGCT of the testis achieving long-term remission and possibly cure in 80–90% of patients [1–4]. The analysis of results of chemotherapy regimens based on a 3 week cycle has allowed the identification of adverse presentations, defined by extent and volume of metastatic disease and by the serum concentration of alpha-foetoprotein (AFP) and beta subunit of human chorionic gonadotrophin (HCG) [5–9]. The Medical Research Council study [7] of 458 patients with metastatic NSGCT identified a subgroup with high marker levels (HCG > 1000 iu/l or AFP > 500 ku/l), associated with extensive disease defined as 'large' or 'very large' volume (Tables 1 and 2). The 3 year survival was 55% compared to 91% in patients with small volume metastatic disease and low serum markers. Testicular germ cell tumours have relatively rapid volume doubling [10] and proliferative capacity [11] and tumour recovery between courses of chemotherapy [12] may explain failure of conventional chemotherapy in some of these patients.

To overcome rapid tumour proliferation as a

Table 1. The Royal Marsden Hospital Staging of testicular tumours

I	No evidence of metastases
I Mk+	Rising serum markers with no other evidence of metastases
II	Abdominal node involvement
A	<2 cm diameter
B	2–5 cm diameter
C	>5 cm diameter
III	Supradiaphragmatic node involvement
M	Mediastinal
N	Supraclavicular/cervical/axillary
O	No abdominal lymphoadenopathy
ABC	As above
IV	Extra-lymphatic metastasis
Lung substage	
L1	≤3 metastases
L2	>3 metastases, all ≤2 cm diameter
L3	>3 metastases, one or more >2 cm diameter
H+	Liver mets
Br+	Brain mets
Bo+	Bone mets

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*Table 2. MRC prognostic groups**

MRC group			RMH stage
I	Small volume	(SV)	I Mk+ IIA IIB IIIA IIIB IVA or IVB L1 or L2
II	Large volume	(LV)	IIC IIIC IVC (L1 or L2)
III	Very large volume	(VLV)	IV L3 H+ Br+ Bo+
High markers		(HM)	BHCG ≥1000 iu/l or AFP ≥500 ku/l
Low markers		(LM)	BHCG <1000 iu/l and AFP <500 ku/l

*MRC (1985).

possible source of treatment failure in adverse subgroups of metastatic NSGCT defined by the MRC analysis we accelerated initial chemotherapy. This intensive induction regimen was based on that described by Wettlaufer *et al.* [13], where in the first 4 weeks of treatment triple drug chemotherapy is administered every 7 days. The toxicity is minimized by dose modifications and by the substitution of vincristine for the more myelosuppressive alternatives, vinblastin [1] or etoposide [2]. After induction chemotherapy further courses of conventional chemotherapy are administered and the overall treatment time is 13 weeks (Fig. 2).

PATIENTS AND METHODS

The staging investigations of patients referred to the Testicular Tumour Unit of the Royal Marsden Hospital following orchidectomy for NSGCT always included full physical examination, assay of serum AFP and HCG, chest X-ray and computerized tomographic (CT) scan of thorax and abdomen. Patients with multiple lung metastases (L3) or high serum HCG concentration (>5000 iu/l) or liver involvement (based on CT evidence) had CNS staging by CT scan of brain and by CSF marker analysis and cytology. Patients were then classified on the RMH staging system (Table 1) and a 'high risk' subgroup was defined by extent of disease and serum marker concentration (Table 3).

Between January 1985 and December 1986, all 29 previously untreated patients with 'high risk' metastatic NSGCT of the testis were entered on the prospective study of Intensive Induction Chemotherapy. Patients' ages ranged from 15 to 52 years (median 25 years). The diagnosis was established by initial orchidectomy in 26 cases and biopsy of an abdominal mass in one case. In two young men with widespread metastases high serum HCG concentrations (37,900 iu/l and 5690 iu/l) and abnormal testicular ultrasound the diagnosis of NSGCT was accepted on clinical grounds. In both patients orchidectomy after chemotherapy revealed mature differentiated teratoma.

The histology of the 26 orchidectomy specimens was reviewed in The Royal Marsden Hospital Department of Histopathology. Seven had malignant teratoma intermediate (MTI) (teratocarcinoma), 11 malignant teratoma undifferentiated (MTU) (embryonal carcinoma), and six malignant teratoma trophoblastic (MTT) (choriocarcinoma pure or with other cell types). Two patients with histologically pure seminoma were regarded as com-

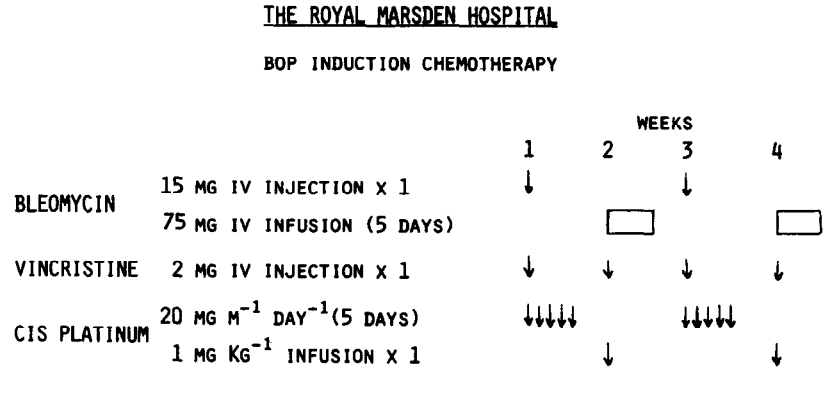

Fig. 1. BOP induction chemotherapy. The figure indicates current recommended dose levels of bleomycin and it should be noted that the first 15 patients in this report were treated with double the indicated doses of this drug.

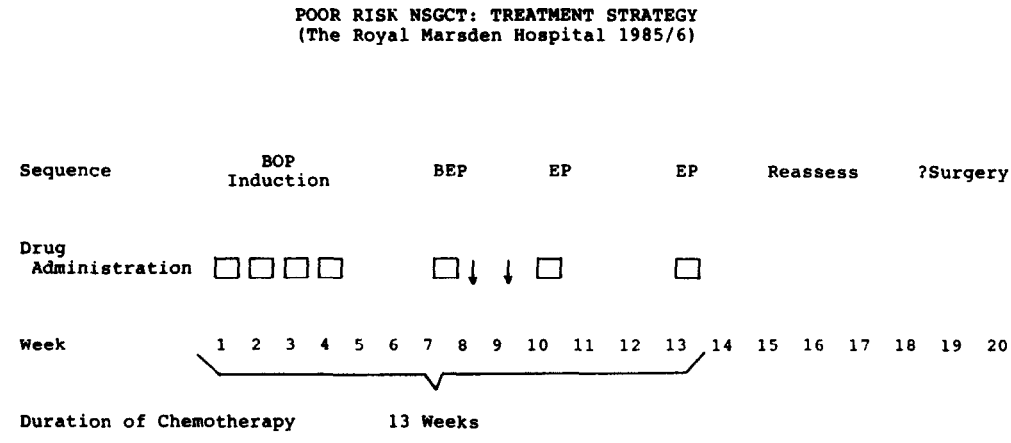

Fig. 2. Overall treatment approach to patients with poor risk NSGCT. For drug details see text and Fig. 1. Square blocks indicate chemotherapy cycles and the arrows indicate the day 9 and 16 bleomycin injections relating to BEP.

Table 3. The Royal Marsden Hospital: malignant non-seminomatous germ cell tumours: definition of high risk sub-group

Stage L3		
Stage C plus	either	AFP >500 ku/l
	or	HCG >1000 iu/l
Liver, bone or brain metastases		
HCG ≥10,000 iu/l or AFP ≥5000 ku/l		
Mediastinal primary		

Table 4. BOP chemotherapy in high risk testicular germ cell tumours: initial extent of disease in 29 patients (The Royal Marsden Hospital 1985/6)

	Number of patients	
Stage IV	27	(93%)
Abdominal nodes >5 cm	16	(55%)
>3 lung metastases (L2 + L3)	21	(78%)
>3 lung metastases >2 cm (L3)	16	(55%)
Liver metastases	7	(24%)
Brain metastases	2	(7%)
Bone metastases	2	(7%)
s.HCG		
>10,000 iu/l	7	(24%)
>1000 iu/l	14	(48%)
s.AFP		
>5,000 ku/l	2	(7%)
>500 ku/l	11	(38%)
One site	3	
Two sites	9	
Three or more sites	17	(59%)

bined tumours, on the basis of multiple 'cannonball' lung metastases with serum AFP of 31 ku/l (normal < 5 ku/l) in one, and in the second case serum HCG of 15,100 iu/l. In four patients, additional seminomatous elements were seen in the primary tumour, one combined with MTI and three combined with MTU.

Details of the extent of disease in the 29 patients are given in Table 4. In addition, one patient had ultrasound evidence of a cardiac mass, one had a splenic deposit and one adrenal deposits seen on CT scanning. One or both serum tumour markers were abnormal in 28 patients, with raised AFP > 5 ku/l) in 23 and raised HCG (>2 u/l) in 25 patients.

Chemotherapy comprised an intensive 4 week induction regimen employing bleomycin, vincristine and cisplatin (Fig. 1) followed by three courses of ((B)EP) [14]. The induction regimen consisted of cisplatin 20 mg/m^2/day, days 1–5 (total 100 mg/m^2), vincristine 2 mg i.v. day 1 and bleomycin 15 mg i.v. day 1 on week 1 and 3. The same drugs were administered on a different schedule during weeks 2 and 4 of intensive induction, as follows: bleomycin infusion of 15 mg/24 h on days 1, 2, 3, 4 and 5 (total 75 mg), vincristine 2 mg i.v. on day 1, cisplatin 1 mg/kg i.v. on day 1. Cisplatin was given with hydration (1 l N saline + 20 mM KCl every 6 h and 200 ml of 10% mannitol for 30 min prior to cisplatin). Magnesium supplementation (20 mM MgCl per litre) was prescribed during infusion chemotherapy and hydrocortisone 100 mg i.v., was given 12 hourly during bleomycin infusions. Following a 2 week gap three further courses of chemotherapy were given on 21 day cycles in the sequence BEP, EP, EP [4]. Drug doses in these cycles were etoposide 120 mg/m^2/day i.v. on days 1, 2 and 3; cisplatin 20 mg/m^2/day on days

1, 2, 3, 4 and 5; bleomycin 30 mg i.v. on days 2, 9 and 16 in the first 15 patients and 15 mg i.v. on days 2, 9 and 16 in the most recent 14 patients. The overall chemotherapy regimen lasted 13 weeks (Fig. 2). Resection of residual masses was then carried out in patients with localized disease and normal serum markers.

Survival and freedom from progressive disease were calculated from the first day of chemotherapy. Complete remission was defined by disappearance of all evidence of disease on CT scanning of thorax, abdomen and other previously involved sites, together with normalization of serum tumour marker concentration.

We initially used bleomycin doses described by Wettlaufer *et al.* [13] (360 mg in the 4 week induction regimen), followed by 30 mg/week × 3 in BEP (total 450 mg in 8 weeks). Because of lung toxicity (*vide infra*), after December 1985 bleomycin doses were halved (Fig. 1) thus the first 15 patients received a high dose bleomycin regimen and the remaining patients received the adjusted dose schedule. Follow up on the reduced dose bleomycin is therefore shorter at 14–26 months (median 19 months).

RESULTS

Of 29 patients treated with intensive BOP induction chemotherapy between January 1985 and December 1986, 27 are evaluable for response, and recurrence-free survival analysis with a follow-up 14–38 (median 24) months. Two patients treated with higher initial bleomycin doses developed fatal pneumonitis 9 weeks after the start of chemotherapy at cumulative bleomycin doses of 450 mg. They were aged 25 and 32 years and had extensive disease with multiple lung metastases. They are included in the overall survival analysis but not in the analyses of relapse-free survival. Thus 85% of 27 evaluable patients have remained free from progressive disease whereas overall cause specific survival in 29 patients was 79%.

Response to chemotherapy (Table 5) was judged both by serum marker assay and radiologically. Prior to treatment 26/27 patients had abnormal serum marker levels. AFP ranged from 31 to 5900 ku/l (mean 1360, median 620) in 17 patients, and HCG ranged from 51 to 379,000 iu/l (mean 63,000, median 5700) in 23 patients. Serum markers normalized in 24 (92%) patients and of these 22 have remained relapse free (Table 5).

Transient marker surges on induction chemotherapy [15] were common occurring in 13 of 24 patients with raised HCG and two of 17 patients with raised AFP. The HCG peak was usually detected between day 8 and 15, with marker level falling below the initial value by day 21. The surge reached 150% of initial marker levels in six patients.

Table 5. Poor risk NSGCT: response to BOP (The Royal Marsden Hospital 1985/6)

Total patients treated		29	
Patients evaluable		27	
Response			
CR	following chemotherapy alone	11	(74%)*
CR	following chemotherapy and surgery	9	
	Persisting mass(es) with normal markers (PMNM)	5	
Relapse			
From CR		0	
from PMNM		2	
Progression during chemotherapy (non remission)		2	
Progression free		3	(85%)*
Status			
Alive, no active disease		22	
Alive, with disease		1	
Dead of malignant disease		3	
Intercurrent disease death (PM-NED)		1	
Dead of treatment toxicity (pneumonitis)		2	

*Percentage of 27 evaluable patients.

A delayed fall of AFP concentration occurred in one patient with a plateau in concentration until day 21 and subsequently a fall to normal values. A further patient presenting with a AFP concentration of 70 ku/l achieved a normal level by week 6 of treatment but subsequently had a rise in AFP to 100 ku/l which resolved spontaneously over a 7 month period and probably represented normal tissue effects.

Following chemotherapy, 11 patients (41%) achieved complete remission on both radiological (CT) and serum marker criteria. Fourteen patients had one or more residual masses with normal serial markers and in nine the residual disease was surgically excised. A further patient had excision of one of multiple residual lung metastases. None of the resected masses contained residual undifferentiated tumour. The histology was mature teratoma (MTD) in five patients and necrosis in five.

Thus 20 patients achieved complete remission following chemotherapy and surgery and a further five have persisting masses with normal marker levels. Two of these five have relapsed, at 4 and 5 months post chemotherapy. Neither responded to further chemotherapy, and one patient died 6 months following relapse. One patient died 1 year after completion of chemotherapy from complications of cystic fibrosis and *post mortem* examination did not reveal any evidence of malignant disease.

Two patients with trophoblastic teratoma (choriocarcinoma) did not achieve marker remission. They had high serum HCG concentrations (373,000 and 114,000 iu/l) with wide-

spread metastatic disease including multiple lung and brain metastases. Despite initial responses marker progression occurred on weeks 9 and 11 of chemotherapy. One patient showed a transient second response to intensive induction chemotherapy. Both patients died 6 and 7 months from start of chemotherapy.

Relapses occurred in two of six patients with serum HCG >100,000 iu/l, three of 21 patients with multiple lung metastases (L2 or L3) (three of 16 with L3 disease), and one of seven patients with liver metastases. All relapses occurred within 7 months of start of chemotherapy. Two recurrences were in the 13 evaluable patients treated with higher bleomycin dose, and two were in the schedule with lower bleomycin dose.

TOXICITY OF TREATMENT

Chemotherapy toxicity is summarized in Table 6. The intensive induction phase of treatment was well tolerated. Most patients experienced nausea and vomiting but this was largely restricted to the first 24 h after *cis*-platinum injections and was controlled with dexamethasone and prochlorperazine. One patient developed peripheral neuropathy (foot drop) which recovered 6 months following chemotherapy. One patient developed malabsorption during week 3, with diarrhoea steatorrhoea and weight loss. This resolved completely after completion of chemotherapy. Bleomycin lung toxicity was seen in 3/16 (19%) patients treated with the initial high dose of bleomycin, and it was fatal in two patients; one patient had dyspnoea associated with CXR and CT changes of pneumonitis on week 13. He was treated with steroids (prednisone 60 mg/day) with rapid symptomatic and slow radiological improvement. Three further patients had asymptomatic CT evidence of pneumonitis. None of the patients receiving lower bleomycin doses developed pulmonary toxicity.

Myelosuppression was uncommon (Table 6). Only two patients developed infection during induction chemotherapy (one of whom had cystic fibrosis). The effect on platelet count was more marked than on white cell count. Renal function was assessed mainly by renal clearance of [^{51}Cr]EDTA. Initial clearances ranged from 73 to 200 ml/min (mean 140 ml/min). Seven (26%) patients had CT evidence of hydronephrosis, one of whom was treated by nephrostomy drainage. Clearances after chemotherapy ranged from 34 to 114 ml/min (mean 83 ml/min) representing a mean reduction to 61% of pre-therapy clearance.

DISCUSSION

We have demonstrated high efficacy of intensive chemotherapy in adverse presentations of metastatic non-seminomatous germ-cell tumours of the testis. Eighty-five per cent of 27 evaluable patients remain free from progression 14 to 38 months (median 24 months) from the start of chemotherapy and cause specific survival in all 29 treated patients was 79%. Disease progression in all four patients occurred early, within 7 months of the start of chemotherapy. This would suggest that the attained responses will be stable. Nevertheless, this report represents a preliminary analysis and further relapses may occur with longer follow-up.

To examine whether the high efficacy of intensive induction was due to selection of patients with a relatively good prognosis, we have compared the Royal Marsden Hospital definition of 'high risk' with the definition from other centres. The Indiana classification identifies 'advanced disease' as primary mediastinal, more than 10 lung metastases per lung field, multiple lung metastases with one greater than 3 cm in diameter, palpable abdominal mass plus lung metastases, liver, bone or brain metastases. These factors were identified on a retrospective analysis of PVB protocols and confirmed

Table 6. *Intensive BOP induction chemotherapy for poor risk NSGCT: toxicity* (29 *patients*) (*The Royal Marsden Hospital* 1985/6)

		Number of patients
Myelosuppression	WBC<1500 nadir	2
	Platelets <80,000 nadir	6
Final renal clearance	<75% of pre-treatment	18
	<50% of pre-treatment	7
	<60 ml/min	6
Pneumonitis	Fatal	2
	Severe, non-fatal	1
	Mild	3
Motor neuropathy		1
Malabsorption		1

on prospective study [16]. Approximately 50% of this category were cured with standard chemotherapy [8]. In the Royal Marsden Hospital definition of advanced disease (Table 3) we have included two patients with large abdominal masses and high serum markers who would have been classified as 'moderate' on the Indiana system. One of these relapsed on the BOP intensive induction regimen. Of 25 evaluable patients in our series who would have been classified as having advanced disease on the Indiana system, 23 (92%) are free from progression.

The Indiana classification of advanced disease was further refined by including the number of elevated tumour markers [16]. This is difficult to apply exactly to our series, since serum LDH was not analysed. The Indiana system identified patients with both advanced disease and two elevated markers to have a 65% 3 year survival and those with advanced disease and three elevated markers to have a 45% 3 year survival. In our series, 15 patients fulfilled the Indiana definition of advanced disease with two elevated markers, although it is likely, of course, that some also had elevated LDH and thus had three elevated markers. Fourteen of these patients (93%) remain free from progression.

In the M.D. Anderson Hospital (M.D.A.) classification [17] of advanced disease, which is less rigorous than the Indiana classification, all patients in the Royal Marsden series would be included. Birch *et al.* [16] report 69/92 (75%) 3 year survival in this group, little different from the 85% seen on BOP induction, and this supports the idea of risk related chemotherapy with little gain from more intensive treatment of less adverse subgroups.

The Medical Research Council Testicular Tumour Subgroup [7] analysed prognostic factors in 458 patients treated with chemotherapy, including 46 patients with 'large volume' disease (see Table 2) and 'high markers' and 117 patients with 'very large volume' disease. Thus 163 patients would have been included in the Royal Marsden Hospital definition of 'advanced disease' and the three year survival of the MRC six centre study was 59%.

An important limitation of these comparisons is that the prognosis of metastatic teratoma has improved over the last decade [7]. The MRC analysis covered the years 1976–1982 and the Indiana analysis from 1978 to 1982 [16]. A more recent multi-centre analysis by the EORTC Genito-urinary Tract Co-operative Group [18] was based on 154 evaluable patients treated with PVB chemotherapy. The endpoint was complete remission on chemotherapy and surgery. Four risk groups were identified with 24 Group 1 patients having 100% complete remission, 73 Group 2 patients having 89% complete remission, 46 Group 3 patients having 41% complete remission and 11 Group 4 patients having 18% complete remission. Combining the two adverse groups, 21 of 59 patients (36%) had a complete remission. In our series of patients treated with BOP induction, 19 patients would fit within Groups 3 or 4 of the EORTC system, of whom 16 (84%) remain free from progression, and 14 (74%) are in complete remission.

There is some evidence that the combination of bleomycin, etoposide and cisplatin (BEP) is more effective than PVB in advanced disease. Pizzocaro *et al.* [19] report prolonged disease free survival in 82.5% of 40 patients with advanced metastatic disease (nodes > 10 cm, lung masses > 5 cm, extrapulmonary spread, AFP > 1000 ng/ml or HCG > 50,000 mIU/ml) and in the prospective randomized comparison of PVB and BEP reported by Williams *et al.* [20] patients with advanced disease on Indiana Staging (*vide supra*) fared better with BEP (survival probability at 2 years 76% vs. 48% with PVB).

The major toxicities of BOP intensive induction were not related to myelosuppression, but were bleomycin associated lung toxicity and cisplatin associated renal toxicity. Bleomycin doses employed in the early part of this study carried too high a risk of pneumonitis. There is increasing evidence that high dose bleomycin is unnecessary in both early [3, 21] and advanced disease [22]. It therefore seems unlikely that the reduction in bleomycin doses in the BOP induction schedule from January 1986 will have a major impact on the success of this approach. However, this will only be answered by longer follow-up. The degree of renal impairment induced by cisplatin was predictable. Clearly in patients where there is a very substantial risk of mortality from malignant disease a degree of treatment related toxicity is acceptable. However, future directions might include attempts to reduce the degree of induced renal damage, either by the use of hypertonic saline infusions [23] or by the use of carboplatin rather than cisplatin [24].

Although our data are too limited for a detailed analysis of prognostic factors, it was notable that neither patient with brain metastases were treated successfully. They presented with other adverse features, including high HCG concentrations and multiple lung metastases. Relapse was probably not due to tumour protection by a blood–brain barrier, since it occurred both systemically and within the CNS. Our current approach is to extend the length of the weekly chemotherapy phase of treatment in this subgroup.

Other approaches to increasing chemotherapy efficacy in poor prognosis metastatic NSGCT have included alternating chemotherapy combinations. Stoter *et al.* [25] reported a comparison of BEP with alternating PVB/BEP, and preliminary analysis has

not revealed any improvement in CR rate. Bosl *et al.* [26] analysed a regime of alternating EP and VAB-6, and concluded that results were equivalent to VAB-6 alone. On the other hand Logothetis *et al.* [27] report excellent results with alternating $CISCA_{II}$ (cyclophosphamide, doxorubicin, cisplatin) and VB_{IV} (vinblastine and bleomycin); 44 of 48 treated patients achieved a prolonged complete remission including 33 of 37 (89%) with bulky or visceral metastatic disease. Forty-five per cent of chemotherapy courses were associated with infectious complications. Also the POMB/ACE regimen (cisplatin, vincristine, methotrexate, bleomycin alternating with actinomycin-D, cyclophosphamide, etoposide) has been reported to yield very good results in advanced metastatic disease [28] with remission in 94% of those with L3 lung disease, 73% with advanced abdominal (C) and lung (L3) disease, 75% with liver metastases and 75% with bone metastases. High tumour markers were adverse prognostic factors and the survival in patients with HCG below 50,000 iu/l and AFP below 500 ku/l was 96% compared to 56% if either marker was above these levels. It is noteworthy that this regimen combined alternation of drug combinations with short intervals between courses.

Also the use of increased cisplatinum dose has been explored. The expected renal toxicity can be mitigated by hypertonic saline infusion [29]. Daugaard and Rorth [30] reported on 29 poor prognosis patients treated with cisplatinum 40 mg/m^2/day × 5 days, etoposide 200 mg/m^2/day × 5 days plus bleomycin 15 mg/m^2 each week. CR rate was very high in previously untreated patients and 77% were alive with no evidence of disease after a median follow-up of 11 months. However, the toxicity was severe with 91% of patients suffering neutropenic fever, with thrombocytopenia <25,000/ml after 75% of cycles, with ototoxicity in 60% of patients and neurotoxicity in 40%. Although the tumour control rate with this approach is high, we believe it important to determine whether equivalent intensification of treatment without high toxicity might be achieved by increasing the frequency of treatment along the lines of our intensive induction schedule.

CONCLUSIONS

Intensive induction chemotherapy appears highly effective in the management of adverse presentations of NSGCT where more traditional chemotherapy schedules lead to disease control in only half of the patients. However, longer follow-up and randomized prospective comparison with alternative regimens will be necessary to confirm the effectiveness of this approach.

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