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Comparative Tolerability of Chemotherapy Regimens for Germ Cell Cancer

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Contents

Abstract

Germ cell tumours, even at an advanced stage, represent a unique model of malignant curable disease since >80% of patients are expected to be cured after appropriate therapy: surgery and radiotherapy in early stages, and chemotherapy and surgery in advanced stages. In advanced stages, serum tumour marker levels as well as extrapulmonary (brain, liver and bone) visceral metastases are the most important prognostic factors that affect treatment modalities.

'Gold standard' regimens for germ cell cancer currently include etoposide plus cisplatin with (BEP) or without (EP) bleomycin. In patients with good risk disease (90% cure rate), the optimal regimen of chemotherapy should combine the best efficacy and the least toxicity. As a result of randomised trials, 3 regimens can be currently recommended: (i) 4 cycles of EP; (ii) 4 cycles of BEP (with etoposide 350 mg/m^2 per cycle); or (iii) 3 cycles of BEP (with etoposide 500 mg/m^2 per cycle). In patients with poor risk disease, 4 cycles of BEP (with etoposide 500 mg/m^2 per cycle) allow a disappointing cure rate of 50%.

The long term toxicity of these regimens (gonadal toxicity and secondary malignancies) appears to be negligible and clearly does not challenge current standard strategies.

Germ cell tumours are rare neoplasms of testicular, ovarian or extragonadal origin. They represent a unique model of curable disease, even at an advanced stage, since more than 80% of patients are expected to be cured after appropriate therapy.[1] Treatment decisions depend on histological type (pure seminoma or nonseminomatous tumours) and extent of disease (early or advanced stages).

Pure seminomas are homogeneous tumours with an absence of marker secretion or slight elevation in serum human chorionic gonadotrophin levels. More than 95% of patients with pure seminoma are cured either by radiotherapy in early stages or by chemotherapy in advanced stages.

Nonseminomatous germ cell tumours are heterogeneous tumours with 4 different histological subtypes (embryonal carcinoma, yolk sac tumour, choriocarcinoma, teratoma) and may be associated with a seminoma component. Elevated serum human chorionic gonadotrophin or α-fetoprotein levels are frequently observed. As nonseminomatous germ cell tumours are not very radiosensitive, chemotherapy and surgery are the mainstay of therapy. In advanced (metastatic) stages, serum human chorionic gonadotrophin, α-fetoprotein and lactate dehydrogenase levels as well as extrapulmonary (brain, liver and bone) visceral metastases are the most important prognostic factors.[2] In poor risk patients (mediastinal primary tumour, extrapulmonary visceral metastases or very high serum tumour marker levels), the expected cure rate is about 50%. Fortunately, only about 15% of patients are included in the poor risk group. Other patients with metastasis have an 85 to 100% chance of cure.

Table I. Standard chemotherapy regimens for germ cell tumours

Regimen and drugs	Dosage
PVB	
Cisplatin	20 mg/m^2/day IV days 1-5
Vinblastine	0.15 mg/kg/day IV day 1-2
Bleomycin	30 U/day IV days 2, 9, 16
	Each cycle every 3 weeks
VAB-6	
Vinblastine	4 mg/m^2 IV day 1
Dactinomycin	1 mg/m^2 IV day 1
Cyclophosphamide	600 mg/m^2 IV day 1
Bleomycin	30U IV day 1 then 20 U/m^2/day continuous IV days 1-3
Cisplatin	120 mg/m^2 IV day 1
	Each cycle every 4 weeks
BEP	
Bleomycin	30 U/day IV days 2, 9, 16
Etoposide	100 mg/m^2/day IV days 1-5 or 120 mg/m^2/day IV days 1-3
Cisplatin	20 mg/m^2/day IV days 1-5
	Each cycle every 3 weeks
EP	
Etoposide	100 mg/m^2/day IV days 1-5
Cisplatin	20 mg/m^2/day IV days 1-5
	Each cycle every 3 weeks
EIP	
Etoposide	75 mg/m^2/day IV days 1-5
Ifosfamide	1200 mg/m^2/day IV days 1-5
Cisplatin	20 mg/m^2/day IV days 1-5
	Each cycle every 3 weeks
VIP	
Vinblastine	0.11 mg/kg/day IV days 1 and 2
Ifosfamide	1200 mg/m^2/day IV days 1-5
Cisplatin	20 mg/m^2/day IV days 1-5
	Each cycle every 3 weeks

IV = intravenous.

1. Historical Perspective

The story of chemotherapy of metastatic germ cell tumours has been clearly marked by the cisplatin revolution. Before the cisplatin era, i.e. before 1975, the literature reported objective responses to a variety of cytotoxic agents (cyclophosphamide, vinblastine or dactinomycin) used alone or in different combinations.[3] However, cure rates were very low. The first important progress was observed with a combination of vinblastine and bleomycin, which allowed long term complete responses.

Following the introduction of cisplatin in chemotherapy regimens, 2 major combinations were developed. Investigators at Indiana University reported a dramatic improvement in the results of chemotherapy with a combination of cisplatin, vinblastine and bleomycin (PVB) [table I]. Among 47 patients who received PVB in a prospective trial published in 1977, 38 (81%) and 27 (57%) patients

achieved a complete response and long term cure, respectively.[4] Subsequent large studies of PVB showed long term cure rates ranging from 68 to 72%.[5,6] Investigators at the Memorial Sloan Kettering Cancer Center in the US simultaneously developed successive protocols that included cyclophosphamide, vinblastine, dactinomycin, bleomycin and cisplatin, the so-called VAB regimens, which have led to the most recent VAB-6 combination (table I). Among 166 patients with germ cell tumours of various origins who were treated with VAB-6, the complete response rate and the long term cure rate were 78 and 71%, respectively.[7] No trial comparing the activities of PVB and VAB-6 has been reported.

With the growing evidence for the excellent single agent activity of etoposide in patients who have failed to respond to first-line chemotherapy, a randomised trial comparing PVB with bleomycin, etoposide and cisplatin (BEP) [table I]) was performed.[8] The results suggested that the BEP regimen had equivalent activity and substantially less toxicity than the PVB regimen. Thus, the BEP regimen (4 cycles) became the standard first-line chemotherapy at Indiana University in the US.

Subsequently, studies have focused on reducing toxicity in patients with good risk characteristics (including advanced seminoma) by omitting bleomycin or replacing cisplatin with carboplatin, and increasing efficacy in patients with poor risk characteristics. Currently, 2 regimens are considered as standard in good risk patients: BEP (3 cycles) and EP (etoposide and cisplatin) [4 cycles]. Carboplatin failed to demonstrate equivalent activity when compared with cisplatin. In patients with poor risk disease, the BEP combination (4 cycles) remains the standard treatment, as no alternative approach has provided better efficacy. After failure of first-line cisplatin-based chemotherapy, the current standard salvage chemotherapy includes vinblastine, ifosfamide and cisplatin (4 cycles). Only 25% of patients are expected to be cured.[1]

2. Comparative Tolerability of Regimens

2.1 Acute Toxicity

2.1.1 Key Trials Establishing the Role of Etoposide

As mentioned in section 1, an important contribution to the establishment of standard germ cell tumour regimens was the randomised trial that compared the PVB regimen (4 cycles) to the BEP regimen (4 cycles).[8] This study was prompted by the efficacy of etoposide in patients with refractory disease, as well as the hope for reducing neuromuscular and/or cardiovascular PVB-induced toxicity. Indeed the PVB combination had been reported to be associated with significant myalgias, abdominal cramps, paraesthesias, Raynaud's phenomenon and even major acute vascular ischaemic events.[4,9-12]

Among 244 evaluable patients with disseminated germ cell tumours, 74 and 83% of patients receiving PVB and BEP became disease free, respectively.[8] The regimens were reported to yield similar myelosuppressive effects and pulmonary toxicity. However, the BEP regimen caused significantly fewer paraesthesias, abdominal cramps and

Table II. Acute toxicity of cisplatin, vinblastine and bleomycin (PVB) versus bleomycin, etoposide and cisplatin (BEP)[8]

Event	PVB (n = 114)	BEP (n = 110)	p-Value
Toxicity (% of patients)			
Paraesthesias			0.02
none	62	77	
mild	27	19	
severe	11	4	
Abdominal cramps			0.0008
none	80	95	
mild	12	3	
severe	8	2	
Myalgias			0.00002
none	81	99	
mild	5	1	
severe	14	0	
Treatment-related deaths (no. of patients)			
Total	7	5	NS
Neutropenic septicaemia	4	2	
Pulmonary fibrosis	2	3	
Small bowel necrosis	1	0	

NS = not statistically significant.

myalgias (table II). Therefore, the recommended protocol for the Eastern Cooperative Oncology Group (ECOG) became the BEP combination.

Concomitantly, investigators at the Memorial Sloan Kettering Cancer Center in the US embarked upon a randomised study between the VAB-6 regimen and the 2-drug combination EP in 164 patients with good prognosis germ cell tumours. With a median follow-up of 24 months, no significant difference was observed in complete response rate (96 versus 93%) and disease-free survival (89 versus 88%). However, patients receiving EP experienced less emesis, less neutropenia, less thrombocytopenia, less magnesium wasting, less mucositis and no pulmonary toxicity as compared with patients included in the VAB-6 arm (table III). EP became the standard regimen of the Memorial Sloan Kettering Cancer Center in the US in good risk patients.[13]

From these 2 trials, it can be concluded that the introduction of etoposide in first-line regimens for germ cell cancer allowed minimisation of toxicity while maintaining efficacy. From then on, the use of vinblastine was restricted to salvage therapy.

Table III. Acute toxicity of the VAB-6 regimen versus etoposide and cisplatin (EP)[13]

Toxicity	VAB-6 (n = 82)	EP (n = 82)	p-Value
Leucopenia (median at nadir) [per μl]	1850	2200	0.06
Thrombocytopenia (median at nadir) [per μl]	95 000	117 000	0.01
Haemoglobin (median at nadir) (g/L)	100	103	NS
Emesis (ml)	2400	1325	0.05
Mucositis (no. of patients)	18	9	0.09
Magnesium (mEq/L)	1.14	1.30	0.0001
Pulmonary toxicity (no. of patients)[a]	13	0	<0.0001
Vascular toxicity (no. of patients)	3	2	NS
Treatment-related deaths (no. of patients)	0	0	

a Number of patients who required deletion of bleomycin because of a decrease in the diffusion capacity of carbon monoxide and/or vital capacity.

NS = not statistically significant; **VAB-6** = vinblastine, dactinomycin, cyclophosphamide, bleomycin, cisplatin.

2.1.2 Bleomycin in Good Risk Patients

For this group of patients, who have an 85 to 100% chance of cure, subsequent trials focused on diminishing the toxicity of chemotherapy regimens (table IV).

Specifically, the role of bleomycin has been questioned with regard to its potentially fatal pulmonary toxicity of pneumonitis and fibrosis. Prior radiation to the lung parenchyma, administration of high fractional concentrations of inspired oxygen, the total dose of bleomycin and the age of the patient have been shown to be factors in the pulmonary toxicity of bleomycin.[22] Enhanced effects of bleomycin have also been observed in patients with decreased renal function caused by cisplatin because of a reduced urinary clearance of bleomycin.[23,24] Studies of pulmonary function in patients with germ cell tumours have shown a significant decrease of total lung capacity, vital capacity and single breath diffusion capacity for carbon monoxide over the period of bleomycin-containing chemotherapy.[22,25] Fortunately, clinically significant symptoms have been reported in less than 20% of patients[26] and the decline in lung function has been reported to be reversible.[27]

The first approach to the reduction of toxicity in patients with good risk germ cell tumours was a randomised study at Indiana University that omitted the fourth cycle of BEP. Among 184 patients who received either 4 (96 patients) or 3 (88 patients) cycles of BEP, therapeutic results appeared equivalent, with 92% of patients experiencing no evidence of disease in either group after a minimal follow-up of 1 year. The investigators concluded that omission of the fourth cycle of BEP was able to significantly reduce the toxicity, cost and inconvenience of treatment without diminishing efficacy.[14] The absence of a statistically significant difference in survival was confirmed by long term follow-up. There have been 4 deaths in each arm. Five patients died of germ cell tumours. One patient died in a vehicle accident without evidence of disease at autopsy. The other 2 deaths were observed in patients who received 3 cycles of BEP and were related to an erosive esophagitis and to

Table IV. Randomised trials establishing the role of bleomycin and carboplatin in patients with good risk germ cell tumours

Regimen	n	Number of cycles	Dose per cycle					Cumulative doses					Efficacy	Toxicity	Selected regimen	Reference
			B (mg)	E (mg/m^2)	V (mg/kg)	P (mg/m^2)	C	B (mg)	E (mg/m^2)	V (mg/kg)	P (mg/m^2)	C				
BEP	96	4	90	500	0	100	0	360	2000	0	400	0	4 BEP = 3 BEP	4 BEP > 3 BEP	3 BEP	14,15
BEP	88	3	90	500	0	100	0	270	1500	0	300	0				
PVB	110	4	30	0	0.3	100	0	360	0	1.2	400	0	4 PVB > 4 PV	4 PVB > 4 PV	4 PVB	16
PV	108	4	0	0	0.3	100	0	0	0	1.2	400	0				
BEP	86	3	30	500	0	100	0	270	1500	0	300	0	3 BEP > 3 EP	3 BEP = 3 EP	3 BEP	17
EP	85	3	0	500	0	100	0	0	1500	0	300	0				
BEP	200	4	30	360	0	100	0	360	1440	0	400	0	4 BEP > 4 EP	4 BEP > 4 EP	4 BEP	18
EP	195	4	0	360	0	100	0	0	1440	0	400	0				
EP	134	4	0	500	0	100	0	0	1500	0	400	0	4 EP > 4 EC	4 EC > 4 EP (haematological)	4EP	19
EC	131	4	0	500	0	0	500 mg/m^2	0	1500	0	0	1500 mg/m^2		4 EP > 4 EC (neurotoxicity)		
BEP	29	3	90	500	0	100	0	270	1500	0	300	0	3 BEP > 4 BEC	3 BEP = 4 BEC	3 BEP	20
BEC	25	4	90	360	0	0	AUC = 5	270	1440	0	0	(AUC = 5) × 4				
BEP	268	4	30	360	0	100	0	90	1440	0	400	0	4 BEP > 4 BEC	4 BEP > 4 BEC	4 BEP	21
BEC	260	4	30	360	0	0	AUC = 5	90	1440	0	0	(AUC = 5) × 4				

AUC = area under curve; **B** = bleomycin; **C** = carboplatin; **E** = etoposide; **P** = cisplatin; **V** = vinblastine; **>** indicates superior to (efficacy) or greater than (toxicity); **=** indicates equal efficacy or toxicity.

Table V. Acute toxicity of cisplatin, vinblastine and bleomycin (PVB) versus cisplatin and vinblastine (PV)[16]

Event (WHO grade)	PVB (n = 110)	PV (n = 108)	p-Value
Toxicity (% of patients)			
Leucopenia (1-4)	50	40	0.04
neutropenic sepsis	28	26	NS
Thrombocytopenia (1-4)	18	8	0.04
Anaemia (3-4)	25	9	0.004
Emesis (2-4)	94	89	NS
Mucositis (1-3)	54	46	NS
Alopecia (2-3)	75	58	0.005
Pulmonary (1-4)	34	0	<0.001
Neuropathy (1-3)	26	31	NS
Auditory (1-3)	26	28	NS
Renal (1-4)	28	18	0.03
Treatment-related deaths (no. of patients)			
Total	6	1	<0.01
Neutropenic septicaemia	4	1	
Pulmonary fibrosis	2	0	

NS = not statistically significant; **WHO** = World Health Organization.

an acute leukaemia.[15] Considering the fact that the power of this study might be too low to detect a slight but possibly important difference between 3 and 4 cycles, the European Organisation for Research and Treatment of Cancer (EORTC) has decided to readdress this question in a larger ongoing trial.

Three trials so far have directly questioned the role of bleomycin.[16-19]. An Australasian group randomly allocated patients to receive either 4 cycles of PVB or 4 cycles of PV.[16] More deaths from malignant disease occurred in the PV arm. However the difference was partly offset by the higher proportion of deaths caused by sepsis or pulmonary toxicity in the PVB arm (6 deaths versus 1 death from sepsis in the PV arm) [table V]. This trial is not relevant today because etoposide-containing regimens are considered to be standard therapy. The ECOG randomised good risk patients to 3 cycles of BEP or 3 cycles of EP. Although no difference was detected in terms of complete responses, an interim analysis revealed an increased number of adverse events (persistent cancer, relapse and death) in the EP arm, which led to early termination of the study. The toxicities were comparable and no clinically significant incidence of pulmonary toxicity was observed in patients treated with BEP.[17] Finally, the EORTC recently published the results of a randomised study comparing 4 cycles of BEP with 4 cycles of EP. In this trial, the dosage of etoposide (350 mg/m^2 every 3 weeks) differed from that used in previous trials (500 mg/m^2 every 3 weeks). Among 395 eligible patients, the complete response rate was inferior with the EP regimen (87 versus 95%, p = 0.0075). Both acute and late pulmonary toxicity and neurotoxicity were significantly greater in the BEP arm. Additionally, Raynaud's phenomenon occurred exclusively in patients treated with bleomycin (table VI). The investigators concluded that, when using etoposide at the dosage of 350 mg/m^2 per cycle, bleomycin could not be omitted without compromising effi-

Table VI. Toxicity in the European Organization for Research and Treatment of Cancer trial comparing 4 cycles of bleomycin, etoposide and cisplatin (BEP) with 4 cycles of etoposide and cisplatin (EP)[18]

Event (WHO grade)	BEP (n = 200)	EP (n = 195)	p-Value
Toxicity (% of patients)			
Leucopenia (3-4)	2	1	NS
neutropenic sepsis	1	1	NS
Thrombocytopenia (4)	3	2	NS
Mucositis (1-3)	17	11	NS
Pulmonary			
acute			
(median % decrease in FVC)	3.8	0	<0.001
(median % decrease in CODC)	20	2	<0.001
late (1-2)	3	0	0.03
Neuropathy (1-3)			
acute	29	13	<0.001
late	13	8	NS
Renal (1-2)	5	6	NS
Treatment-related deaths (no. of patients)			
Total	2	0	NS
Neutropenic septicaemia	0	0	
Pulmonary fibrosis	2	0	

CODC = carbon monoxide diffusion capacity; **FVC** = forced vital capacity; **NS** = not statistically significant; **WHO** = World Health Organization.

cacy, although efforts aiming at reducing toxicity should be continued.[18]

As a result of these randomised trials, 3 regimens can be currently recommended for treatment of good risk patients: (i) 4 cycles of EP; (ii) 4 cycles of BEP (with etoposide 350 mg/m^2 per cycle); or (iii) 3 cycles of BEP (with etoposide 500 mg/m^2 per cycle). No direct comparison between these regimens has been published so far. Investigators of the Genitourinary Group of the French Federation of Cancer Centers have embarked upon a randomised trial comparing 4 cycles of EP with 3 cycles of BEP (with etoposide 500 mg/m^2 per cycle). Indeed, a retrospective study in 58 patients suggested that 4 cycles of EP could yield inferior results compared with 3 cycles of BEP.[28] Other ongoing randomised trials aim to address the role of dosage reductions of either bleomycin or etoposide. In terms of bleomycin-induced adverse effects, it is noteworthy that clinically significant pulmonary toxicity has only been reported with cumulative doses beyond 300 mg/m^2 in randomised trials. Therefore, the complete omission of bleomycin may not be required to further reduce toxicity.

2.1.3 Carboplatin in Good Risk Patients

The activity of carboplatin-containing regimens was observed in pilot studies, and carboplatin has a toxicity profile better than cisplatin. Another way to reduce toxicity could have been the replacement of cisplatin by carboplatin. However, all 3 randomised trials published so far have clearly shown the superiority of cisplatin-based regimens over carboplatin-based regimens (table IV). Regarding toxicity, haematological adverse effects were more pronounced in patients treated with carboplatin-based regimens, whereas neurotoxicity and renal toxicity occurred predominantly with cisplatin-based regimens.[19,21]

2.1.4 Poor Risk Patients

Different strategies have been investigated to improve the disappointing 50 to 70% cure rate of patients with poor risk disease, including the introduction of new drugs, the sequential alternation of chemotherapy regimens and/or increases in drug dose-intensities (table VII).

TableVII

Table VII. Randomised trials in patients with poor risk germ cell tumours

Regimen	n	Cisplatin		Ifosfamide		Etoposide		Bleomycin TD (mg)	Efficacy	Toxicity	Selected regimen	Reference
		TD (mg/m^2)	DI (mg/m^2/wk)	TD (g/m^2)	DI (g/m^2/wk)	TD (mg/m^2)	DI (mg/m^2/wk)					
BEP	125	400	33	0	0	2000	166	360	BEP = EIP	EIP > BEP	BEP	29
EIP	128	400	33	24	2	2000	166	0				
BEP	118	400	33	0	0	1440	166	360	BEP = PVB/BEP	PVB/BEP > BEP	BEP	30
PVB/BEP	116	400	33	0	0	720	83	360				
PVB	18	400	33	0	0	0	0	360	PVBE > PVB	PVBE > PVB	PVBE	31
PVBE	34	600-800	66	0	0	1500-2000	166	270-360				
BEP	78	400	33	0	0	2000	166	360	BEP = BEdP	BEdP > BEP	BEP	32
BEdP	76	822	66	2	2	2000	166	360				
BEP	185	600	33	0	0	3000	166	360	BEP = BOP/EIP	BOP/EIP > BEP	BEP	33
BOP/EIP	186	600	50	15	1.8	900	100	300				

B = bleomycin; **DI** = dose intensity; **dP** = double dose cisplatin; **E** = etoposide; **I** = ifosfamide; **O** = vincristine **P** = cisplatin; **TD** = total dose; **V** = vinblastine; **wk** = week; **>** indicates superior to (efficacy) or greater than (toxicity); **=** indicates equal efficacy or toxicity.

The ECOG studied whether ifosfamide in place of bleomycin (i.e. the EIP regimen) was more active in combination therapy.[29] BEP and EIP produced comparable response rates (60 versus 63%) and failure-free survival (60 versus 64%). The EIP arm was associated with significantly greater haematological and genitourinary toxicity (table VIII). Similar results were observed in an EORTC study comparing the same regimens.[34]

The EORTC compared the efficacy and toxicity of 4 cycles of standard BEP with 4 alternating cycles of BEP plus PVB.[30] There was no significant difference in complete response rate (72 versus 76%) and disease-free survival at an average follow-up of 6 years. The alternating regimen was associated with greater haematological, mucosal and neurological toxicity (table IX).

Following the results from *in vitro* experiments and early clinical trials suggesting a dose-response relationship for cisplatin in germ cell tumours, investigators at the US National Cancer Institute developed a new combination of double-dose cisplatin, vinblastine, bleomycin and etoposide (PVBE).[35] In a randomised trial comparing PVBE with standard PVB, a higher response rate and less frequent relapses were observed in the PVBE arm.[31] Gastrointestinal and haematological toxicities were increased with the more aggressive therapy. However, the apparent superiority of the PVBE regimen may have been due to confounding factors, including the doubled dose of cisplatin and the addition of etoposide. The role of cisplatin dose intensity was directly assessed when patients with poor risk characteristics were randomised to receive either standard BEP or the same combination with double-dose cisplatin in a subsequent randomised trial.[32] No significant difference was detected between the 2 arms in relation to response rate (73 versus 68%) or disease-free survival (61 versus 63%). The high dose arm was associated with significantly greater toxicity, including myelosuppression, emesis, ototoxicity and neurotoxicity (table X).

Another way to increase the cisplatin dose intensity is the development of intensive induction chemotherapy regimens, delivering drugs at reduced intervals between cycles. Such an approach [using bleomycin, vincristine and cisplatin (BOP)/EIP] was reported to yield a 63% disease-free rate in 91 patients.[36] However, a randomised comparison between a BEP/EP regimen and BOP/EIP did not show any significant difference in efficacy, with a 1-year failure-free survival of 60% and 53%, respectively.[32] World Health Organization grade 3/4 leu-

Table VIII. Acute toxicity of bleomycin, etoposide and cisplatin (BEP) versus etoposide, ifosfamide and cisplatin (EIP)[29]

Event (WHO grade)	BEP (n = 148)	EIP (n = 151)	p-Value
Toxicity (% of patients)			
Haematological			<0.001
(grade 3)	39	28	
(grade 4)	34	60	
Gastrointestinal (3-4)	7	9	NS
Neuropathy (1-4)	7	8	NS
Pulmonary (1-4)	5	5	NS
Genitourinary (1-4)			0.036
renal toxicity	1	6	
haematuria	0	2	
Treatment-related deaths (no. of patients)			
Total	6	5	NS
Neutropenic septicaemia	3	4	
Pulmonary failure	3	0	
Cerebral haemorrhage	0	1	

NS = not statistically significant; **WHO** = World Health Organization.

Table IX. Acute toxicity of bleomycin, etoposide and cisplatin (BEP) versus alternating cycles of BEP and cisplatin, vinblastine and bleomycin (PVB)[30]

Event (WHO grade)	BEP (n = 118)	BEP/PVB (n = 116)	p-Value
Toxicity (% of patients)			
Leucopenia (4)	5	28	<0.001
neutropenic fever	5	16	0.006
Thrombocytopenia (4)	1	10	0.001
Gastrointestinal (1-4)	97	98	NS
Neuropathy (1-4)	25	47	<0.001
Mucositis (1-4)	16	28	<0.05
Pulmonary (1-4)	3	3	NS
Treatment-related deaths (no. of patients)			
Total	NR	NR	NS

NR = not reported; **NS** = not statistically significant; **WHO** = World Health Organization.

copenia was more frequent with BOP/EIP than with BEP/EP (68 versus 38%, p = 0.001), as was grade 3/4 thrombocytopenia (52 versus 25%, p = 0.001). Febrile neutropenia occurred more frequently with BOP/EIP than with BEP/EP (35 versus 18%, p = 0.001). Bodyweight loss was also more pronounced on BOP/EIP than on BEP/EP (p = 0.0001). No other significant differences between the 2 regimens in terms of nonhaematological toxicity were reported.

A subset of patients included in this trial were secondarily randomised to receive or not receive granulocyte colony-stimulating factor with the aim of assessing the possible impact of granulocyte colony-stimulating factor on chemotherapy delivery and outcome. The addition of granulocyte colony-stimulating factor led to a significantly higher relative dose-intensity for etoposide and cisplatin in both arms, and for ifosfamide in patients who received the BOP/EIP schedule, without effect on failure-free and overall survival. Regarding chemotherapy-related adverse effects, neutropenic fever and treatment-related death rates were significantly lower in the granulocyte colony-stimulating factor arm (table XI). However, this observation was confined to the BOP/EIP regimen. The investigators concluded that these results do not support the use of granulocyte colony-stimulating factor during standard chemotherapy with BEP.[37]

Table X. Acute toxicity of bleomycin, etoposide and cisplatin (BEP) versus BEP with a double dose of cisplatin (BEdP)[32]

Event (WHO grade)	BEP (n = 77)	BEdP (n = 76)	p-Value
Toxicity (% of patients)			
Leucopenia (3-4)	16	36	<0.001
neutropenic fever	16	50	<0.001
Thrombocytopenia (1-4)	10	58	<0.001
Red blood cell transfusions	25	63	<0.001
Gastrointestinal (3-4)	4	26	<0.001
Neuropathy (3-4)	1	26	<0.001
Ototoxicity (3-4)	0	32	<0.001
Renal (3-4)	3	3	NS
Treatment-related deaths (no. of patients)			
Total	2	3	NS
Neutropenic septicaemia	0	2	
Pulmonary fibrosis	1	0	
Congestive heart failure	1	1	

NS = not statistically significant; **WHO** = World Health Organization.

Only 1 randomised study of high dose chemotherapy with haemopoietic progenitor cell support has been reported so far in the first-line treatment of patients with poor risk disease. 115 patients were randomised to receive either 3 to 4 cycles of the PVBE regimen or 2 cycles of PVBE followed by a single high dose chemotherapy regimen including cisplatin, cyclophosphamide and etoposide with autologous bone marrow transplant support. No evidence of benefit to the high dose arm was observed.[38] No data about comparative toxicities are available so far.

2.2 Long Term Toxicity

2.2.1 Gonadal Toxicity

As cisplatin-based chemotherapy has clearly improved the cure rates of young patients who have not yet established a family, the long term impact of treatment on gonadal function has assumed increasing clinical importance. Gonadal toxicity has mainly been evaluated by measurement of sperm cell concentration and follicle stimulating hormone serum levels for exocrine gonadal function, and by testosterone and luteinizing hormone serum levels for endocrine function.

Regarding spermatogenesis, most patients undergoing chemotherapy become azoospermic about 8 weeks after the onset of treatment because of the cytotoxic effect on rapidly proliferating spermatogonia. A simultaneous increase in follicle stimulating hormone levels is observed. However, the severity and duration of long term impairment of spermatogenesis is related to the number of stem cell spermatogonia that are destroyed. A number of studies have focused on the long term effects of cisplatin-based chemotherapy on spermatogenesis (table XII). The median sperm count was in the range 0 to 82 million/ml after a median follow-up of 24 to 79 months.[39-49] This large variation could be related to the varying dose of chemotherapy, especially the cumulative dose of cisplatin, and the duration of the follow-up period. In accordance

Table XI. Acute toxicity of intensive induction chemotherapy regimens and the role of granulocyte colony-stimulating factor[37]

Event (WHO grade)	Without G-CSF		With G-CSF	
	BEP/EP (n = 64)	BOP/EIP (n = 65)	BEP/EP (n = 63)	BOP/EI (n = 65)
Toxicity (% of patients)				
Leucopenia				
grade 1-2	47	9	24	34
grade 3	36	37	11	18
grade 4	13	49	13	18
neutropenic fever	13	46	14	25
Thrombocytopenia				
grade 1-2	30	25	35	14
grade 3	6	15	22	23
grade 4	9	33	21	38
Mucositis				
grade 1-2	30	28	22	28
grade 3	3	5	6	6
grade 4	0	5	0	0
Pulmonary				
grade 1-2	16	14	25	17
grade 3	3	2	0	5
grade 4	0	5	3	2
Treatment-related deaths (no. of patients)				
Total	15		5	
Neutropenic septicaemia	9		3	
Pulmonary fibrosis	3		0	
Pulmonary embolism	1		0	
Perioperative haemorrhage	1		2	
Acute myeloid leukaemia	1		0	

BEP/EP = bleomycin, etoposide and cisplatin/etoposide and cisplatin; **BOP/EIP** = bleomycin, vincristine and cisplatin/etoposide, ifosfamide and cisplatin; **G-CSF** = granulocyte colony-stimulating factor; **WHO** = World Health Organization.

with the impaired semen quality, a persistent increase in serum follicle stimulating hormone levels was observed in most (19 to 95%) patients. When evaluating the long term impairment of gonadal function caused by cytotoxic chemotherapy, it is important to remember that many patients with germ cell tumours show unequivocal evidence of impaired spermatogenesis before any treatment[50,51] or after orchidectomy and before chemotherapy.[40,44,45,52-54] Indeed, the pretreatment sperm count has been shown in several reports to be correlated with subsequent gonadal function.[55-57] The cumulative dose of cisplatin was the other significant prognostic variable observed in a number of studies.[45,48,57] In patients who received a cumulative dose of up to 400 mg/m^2, the sperm concentration, rate of azoospermia and serum follicle stimulating hormone levels did not appear to be significantly different from those of patients treated without chemotherapy. Regarding the individual regimens, there are no data that allow a reliable comparison between gonadal toxicity after PVB and BEP. The only report[58] suggesting that the BEP combination could be more toxic for long term gonadal function was not confirmed by 2 other studies.[59,60] In contrast, 1 report found that the use of a vinca alkaloid was correlated with impairment of sperm recovery, whereas the use of etoposide was not.[57]

In summary, the most reliable prognostic factor associated with sperm recovery is the pretreatment sperm count in patients treated with standard germ cell tumour regimens (3 to 4 cycles). The probability of recovering spermatogenesis has been assessed at 75% and 45% at 3 years for patients with normospermia/oligospermia and azoospermia before chemotherapy, respectively.[57]

Regarding the endocrine function, increased serum luteinizing hormone levels have been seen in up to 86% of patients more than 2 years after chemotherapy, indicating persistent dysfunction of Leydig's cells, despite normal testosterone levels in most patients (table XII). This compensated insufficiency was still observed up to 60 months after chemotherapy in a recent report.[61] Once again, such a phenomenon has been shown to be significantly influenced by the cumulative dose of cisplatin.[48]

What is the impact of these observations on the reproductive capacity of patients with germ cell tumours? Evaluation of the contribution of chemotherapy is hampered by a lack of knowledge about the prevalence of infertility in the general population, and by the influence of the disease itself and other treatments (such as retroperitoneal surgery) on the risk of infertility. In a retrospective review

Table XII

of 12 long term follow-up studies of patients treated with cisplatin-based chemotherapy, 145 (21%) of 680 patients were reported to achieve paternity.[62] As the number of patients actually seeking fatherhood was not assessed, it is impossible to draw firm conclusions regarding the effective reproductive capacities of patients with germ cell tumours after chemotherapy. There is no evidence of an elevated risk of malformations in children fathered by patients with germ cell tumours.[63,64]

2.2.2 Secondary Malignancies

A number of reports have addressed the issue of secondary non–germ cell malignancies in patients with germ cell tumours.[65-70] In general, studies that included more than 1000 patients have indicated a significantly (2-fold) elevated overall risk for the occurrence of solid tumours as well as leukaemias (table XIII). However, radiotherapy is associated with a 2- to 3-fold increased risk for secondary solid tumours, and there is currently no firm evidence that chemotherapy significantly elevates the risk for secondary solid cancers.[71] Regarding the development of secondary leukaemias, 3 series with the largest median follow-up (8 to 9.5 years) have found a significantly elevated relative risk, ranging from 2.4 to 5.2.[65,69,70] It is noteworthy that the development of leukaemias independent from therapy has been described in patients with primary mediastinal germ cell tumours.[71-73] As the isochromosome 12p, a typical cytogenetic marker for testicular cancer, has been identified in the leukaemic cells, the occurrence of such leukaemias following mediastinal germ cell tumours is regarded as a biological relationship between 2 diseases and not a therapy-induced adverse effect.

In recent years, specific concern has been raised by reports of a particular role of etoposide in the development of leukaemias. Secondary leukaemias induced by alkylating agents occur most frequently after an interval of 5 to 7 years, are preceded by a preleukaemic myelodysplastic phase and have common cytogenetic abnormalities of chromosomes 5 and 7. In contrast, the type of leukaemias observed after treatment with topoisomerase II inhibitors, such as etoposide, are characterised

Table XII. Long term gonadal function after cisplatin-based chemotherapy

Regimen	n	Median total dose of platinum (mg/m^2)	Median follow-up (months)	Median sperm count ($\times 10^6$/ml)	Patients [number (%)] with				Reference
					azoospermia	FSH > N	LH > N	T < N	
VB ± P	24	NR	34	40 (0-108)	2/11 (18)	13/23 (56)	7/23 (30)	0/16 (0)	39
PVB ± A	28	300 (200-600)	40 (27-80)	11.3 (0-100)	4/24 (17)	15/28 (54)	12/28 (43)	7/28 (25)	40
PVB ± A	18	400 (300-700)	24 (1-51)	0 (0-126)	8/13 (62)	11/18 (61)	12/18 (67)	2/18 (11)	41
VAB-6	22	360 (360-540)	24 (9-54)	NR	NR	14/22 (64)	19/22 (86)	0/20 (0)	42
PVB	54	400	24	38 (0-175)	7/25 (28)	NR	NR	NR	43
PVB	21	487 (346-614)	24 (18-29)	82 (0-292)	NR	NR	NR	NR	44
PVB	22	600	64 (42-100)	0.35 (0-78)	6/22 (27)	19/22 (86)	13/22 (59)	3/22 (14)	45
PVB ± E	27	350 (150-680)	30 (7-63)	29 (0-150)	5/24 (21)	18/24 (75)	16/24 (67)	0/24 (0)	46
Mainly PVB or BEP	74	400 (80-780)	52 (13-125)	NR	NR	14/74 (19)	14/74 (19)	23/72 (32)	47
Standard BEP	33	400 (307-450)	79 (61-103)	5.8 (0-83)	5/27 (18)	22/30 (73)	8/30 (27)	1/30 (0)	48
High dose BEP	21	618 (486-1197)	59 (31-103)	0 (0-69.5)	8/17 (47)	20/21 (95)	9/21 (43)	2/21 (1)	48
Mainly PVB or BEP	63	360 (360-1050)	58 (15-159)	NR	NR	40/63 (63)	21/63 (33)	6/63 (10)	49

A = doxorubicin; **B** = bleomycin; **E** = etoposide; **FSH** = follicle stimulating hormone; **LH** = luteinizing hormone; **N** = normal values; **NR** = not reported; **P** = cisplatin; **T** = testosterone; **V** = vinblastine; **VAB-6** = vinblastine, dactinomycin, cyclophosphamide, bleomycin and cisplatin.

Table XIII

by a short latent period and balanced chromosomal translocations involving chromosome 11.[74] The cumulative dose of etoposide has been claimed to play a key role in the development of secondary leukaemias. In a Danish report, all 5 patients who developed myeloid leukaemias were among those 82 patients who had received more than 2000 mg/m^2 of etoposide, whereas no leukaemia was observed among 130 patients who had received lower cumulative doses.[75] Four subsequent studies have been published of patients treated with standard dose chemotherapy, i.e. containing etoposide at doses ≤2000 mg/m^2 (table XIV). Among 1868 patients, 11 cases of secondary leukaemia were reported, 7 of which showed typical features of etoposide-related leukaemia. Based on an annual incidence of 3 to 4 nonlymphocytic leukaemias per 100 000 persons, the rate of secondary etoposide-related leukaemia seems to be elevated by a factor of 15 to 25.[71] However, in the light of the high cure rate induced by etoposide-containing regimens, the risk for the individual patient appears negligible and does not challenge current standard strategies.

2.2.3 Other Long Term Toxicity

Peripheral neuropathy is a common adverse effect of vinca alkaloids and cisplatin. Long term symptoms of neuropathy following chemotherapy for testicular cancer – mainly with PVB – have been reported in 12 to 68% of patients.[79-84] In a careful evaluation using the determination of the vibration threshold, an incidence of up to 80% was found up to 10 years after treatment.[81] No other risk factors for the development of peripheral neuropathy apart from the cumulative dose of cisplatin were identified. Patients additionally receiving vinca alkaloids during their treatment are at higher risk for the occurrence of reversible, but not persistent, neuropathy.[84]

Another specific problem with cisplatin administration is ototoxicity with cochlear damage. A high-tone frequency loss is found in about one-third of patients. However, this deficiency is often subclinical. This toxicity is irreversible and is related to the cumulative total dose of cisplatin.[85] It is possible that individual susceptibility or other

Table XIII. Risk of secondary malignancies in patients with germ cell tumours[71]

No. of patients	Median follow-up (years)	Secondary solid tumours			Secondary leukaemias			Reference
		number	relative risk (95% CI)	significance	number	relative risk (95% CI)	significance	
1 446	8.0	104	2.1 (1.7-2.5)	S	8	5.2 (2.3-10)	S	65
2 013	6.8	22	0.7 (0.5-1.0)	NS	22	2.5 (0.4-7.9)	NS	66
17 730	6.4	480	1.3 (NR)	S	9	2.0 (NR)	NS	67
1 025	5.1	14	3.1 (1.2-6.0)	S	1	2.7 (0.9-4.6)	NS	68
6 187	9.5	459	1.6 (1.5-1.8)	S	18	2.4 (1.4-3.7)	S	69
1 909	7.7	78	1.6 (1.3-2.1)	S	4	5.1 (1.4-13)	S	70

CI = confidence interval; **NR** = not reported; **NS** = not statistically significant; **S** = statistically significant.

Table XIV. Risk of secondary leukaemias in patients with germ cell tumours treated with standard doses of etoposide (≤2000 mg/m^2)

Patients	Median follow-up (years)	Number of secondary leukaemias		Reference
		total	etoposide-related[a]	
130	5.4	0	0	75
221	5.5	1	1	68
343	≥5	2	1	76
538	4.9	2	2	77
636	>5	6	3	78

a Based on morphology and cytogenetic analysis.

factors such as age, mode of administration of cisplatin or dose per course could be involved in determining the extent of VIIIth nerve damage.[86]

The most common vascular toxicity is Raynaud's phenomenon. Although this symptom has been observed following bleomycin alone,[87] it has more often been documented in patients receiving vinblastine and bleomycin.[88] The addition of cisplatin to vinblastine and bleomycin increases the incidence. Up to 40% of patients treated with either vinblastine plus bleomycin or PVB develop this phenomenon.[10] Although the exact mechanism of vascular alteration is unknown, a role for cisplatin-induced hypomagnesaemia was suggested.[89] When the arterial vasoconstrictor response to cold in the fingers is studied, an exaggerated reaction can be detected after several years, suggesting a prolonged vasospastic adverse effect, even in patients without finger symptoms.[90] The frequency of Raynaud's phenomenon was not altered after replacement of vinblastine by etoposide.[8] However, the omission of bleomycin clearly reduces this adverse effect, as no Raynaud's phenomenon has been observed at the Memorial Sloan Kettering Cancer Center with the EP combination.[13]

Major vascular events, such as acute myocardial infarction or cerebral ischaemic events, were also reported after PVB.[11,12,91] The relative infrequency of these events and the presence of confounding factors make a definite cause-effect relationship difficult to establish.[92] Recent studies suggested that hypercholesterolaemia and excess bodyweight might represent long term risk factors for these cardiovascular complications.[93,94] More data are needed to draw firm conclusions.

3. Conclusions

The evaluation of the comparative acute and long term toxicities of germ cell tumour regimens is a major end-point of clinical trials for patients with metastatic disease. With regard to the high cure rate observed in patients with good risk disease, the optimal regimen of chemotherapy should combine the best efficacy and the least acute and long term toxicity. In patients with poor risk disease, the major end-point remains the improvement in cure rates. Regarding long term adverse effects, the risk for the individual patient appears to be negligible and clearly does not challenge current standard strategies. In patients with stage I disease, i.e. disease confined to the testis, recent data have suggested the efficacy of 2 cycles of BEP in the adjuvant setting.[95,96] More data focusing on long term toxicity will be required to assess the harmlessness of adjuvant chemotherapy.

References

1. Culine S, Kramar A, Biron P, et al. Chemotherapy in adult germ cell tumors. Crit Rev Oncol Hematol 1996; 22: 229-63
2. International Germ Cell Cancer Collaborative Group. International germ cell consensus prognostic classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997; 15: 594-603
3. Droz JP, Culine S. New prospects for the treatment of germ-cell tumours. Exp Opin Invest Drugs 1998; 7: 1139-57
4. Einhorn LH, Donohue J. Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 1977; 87: 293-8
5. Stoter G, Sleyfer DT, ten Bokkel Huinink WW, et al. High-dose versus low-dose vinblastine in cisplatin-vinblastine-bleomycin combination chemotherapy of non-seminomatous testicular cancer: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. J Clin Oncol 1986; 4: 1199-206
6. Levi JA, Thomson D, Sandeman T, et al. A prospective study of cisplatin-based combination chemotherapy in advanced germ cell malignancy: role of maintenance and long-term follow-up. J Clin Oncol 1988; 6: 1154-60
7. Bosl GJ, Gluckman R, Geller NL, et al. VAB-6: an effective chemotherapy regimen for patients with germ-cell tumors. J Clin Oncol 1986; 4: 1493-9
8. Williams SD, Birch R, Einhorn LH, at al. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 1987; 316: 1435-40
9. Samson MK, Fisher R, Stephens RL, et al. Vinblastine, bleomycin and cis-diamminedichloroplatinum in disseminated

testicular cancer: response to treatment and prognostic correlations. Eur J Cancer 1980; 16: 1359-66
10. Vogelzang NJ, Bosl GJ, Johnson K, et al. Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. Ann Intern Med 1981; 95: 288-92
11. Doll DC, List AF, Greco FA, et al. Acute vascular ischemic events after cisplatin-based combination chemotherapy for germ-cell tumors of the testis. Ann Intern Med 1986; 105: 48-51
12. Samuels BL, Vogelzang NJ, Kennedy BJ. Severe vascular toxicity associated with vinblastine, bleomycin, and cisplatin chemotherapy. Cancer Chemother Pharmacol 1987; 19: 253-6
13. Bosl GJ, Geller NL, Bajorin D, et al. A randomized trial of etoposide + cisplatin versus vinblastine + bleomycin + cisplatin + cyclophosphamide + dactinomycin in patients with good-prognosis germ cell tumors. J Clin Oncol 1988; 6: 1231-8
14. Einhorn LH, Williams SD, Loehrer PJ, et al. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol 1989; 7: 387-91
15. Saxman SB, Finch D, Gonin R, et al. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: the Indiana University experience. J Clin Oncol 1998; 16: 702-6
16. Levi JA, Raghavan D, Harvey V, et al. The importance of bleomycin in combination chemotherapy for good-prognosis germ cell carcinoma. J Clin Oncol 1993; 11: 1300-5
17. Loehrer PJ, Johnson D, Elson P, et al. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. J Clin Oncol 1995; 13: 470-6
18. De Wit R, Stoter G, Kaye SB, et al. Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. J Clin Oncol 1997; 15: 1837-43
19. Bajorin DF, Sarosdy MF, Pfister DG, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. J Clin Oncol 1993; 11: 598-606
20. Bokemeyer C, Köhrmann O, Tischler J, et al. A randomized trial of cisplatin, etoposide and bleomycin (PEB) versus carboplatin, etoposide and bleomycin (CEB) for patients with 'good-risk' metastatic non-seminomatous germ cell tumors. Ann Oncol 1996; 7: 1015-21
21. Horwich A, Sleijfer DT, Fossa SD, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer trial. J Clin Oncol 1997; 15: 1844-52
22. Wolkowicz J, Sturgeon J, Rawji M, et al. Bleomycin-induced pulmonary function abnormalities. Chest 1992; 101: 97-101
23. Van Barneveld PWC, Sleijfer DT, Van der Mark TW, et al. Influence of platinum-induced renal toxicity in bleomycin-induced pulmonary toxicity in patients with disseminated testicular carcinoma. Oncology 1984; 41: 4-7
24. Sleijfer DT, Van der Mark TW, Schraffordt Koops H, et al. Enhanced effects of bleomycin on pulmonary function disturbances in patients with decreased renal function due to cisplatin. Eur J Cancer 1996; 32A: 550-2
25. Van Barneveld PWC, Veenstra G, Sleijfer DT, et al. Changes in pulmonary function during and after bleomycin treatment in patients with testicular carcinoma. Cancer Chemother Pharmacol 1985; 14: 168-71
26. McKeage MJ, Evans BD, Atkinson C, et al. Carbon monoxide diffusing capacity is a poor predictor of clinically significant bleomycin lung. J Clin Oncol 1990; 8: 779-83
27. Lehne G, Johansen B, Fossa SD. Long-term follow-up of pulmonary function in patients cured from testicular cancer with combination chemotherapy including bleomycin. Br J Cancer 1993; 68: 555-8
28. Culine S, Théodore C, Terrier-Lacombe MJ, et al. Are 3 cycles of bleomycin, etoposide and cisplatin or 4 cycles of etoposide and cisplatin equivalent optimal regimens for patients with good risk metastatic germ cell tumors of the testis? The need for a randomized trial. J Urol 1997; 157: 855-9
29. Nichols CR, Catalano PJ, Crawford ED, et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group and Leukemia Group B study. J Clin Oncol 1998; 16: 1287-93
30. De Wit R, Stoter G, Sleijfer DT, et al. Four cycles of BEP versus an alternating regime of PVB and BEP in patients with poor-prognosis metastatic testicular non-seminoma; a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. Br J Cancer 1995; 71: 1311-4
31. Ozols RF, Ihde DC, Linehan WM, et al. A randomized trial of standard chemotherapy *vs* a high dose chemotherapy regimen in the treatment of poor prognosis metastatic nonseminomatous germ-cell tumors. J Clin Oncol 1988; 6: 1031-40
32. Nichols CR, Williams SD, Loehrer PJ, et al. Randomized study of cisplatin dose intensity in poor-risk germ cell tumors: a Southeastern Cancer Study Group and Southwest Oncology Group protocol. J Clin Oncol 1991; 9: 1163-72
33. Kaye SB, Mead GM, Fossa S, et al. Intensive induction-sequential chemotherapy with BOP/VIP compared with treatment with BEP/EP for poor-prognosis metastatic nonseminomatous germ cell tumor: a randomized Medical Research Council/European Organization for Research and Treatment of Cancer study. J Clin Oncol 1998; 16: 692-701
34. De Wit R, Stoter G, Sleijfer DT, et al. Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. Br J Cancer 1998; 78: 828-32
35. Ozols RF, Deisseroth AB, Javadpour N, et al. Treatment of poor prognosis nonseminomatous testicular cancer with a 'high-dose' platinum combination chemotherapy regimen. Cancer 1983; 51: 1803-7
36. Lewis CR, Fossa SD, Mead G, et al. BOP/VIP – a new platinum-intensive chemotherapy regimen for poor prognosis germ cell tumours. Ann Oncol 1991; 2: 203-11
37. Fossa SD, Kaye SB, Mead GM, et al. Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. J Clin Oncol 1998; 16: 716-24
38. Droz JP, Pico JL, Biron P, et al. No evidence of a benefit ofearly intensified chemotherapy with autologous bone marrow transplantation in first line treatment of poor risk non seminomatous germ cell tumors: preliminary results of a randomized trial [abstract]. Proc Am Soc Clin Oncol 1992; 11: 197
39. Lange PH, Narayan P, Vogelzang NJ, et al. Return of fertility after treatment for nonseminomatous testicular cancer: changing concepts. J Urol 1983; 129: 1131-5

40. Drasga RE, Einhorn LH, Williams SD, et al. Fertility after chemotherapy for testicular cancer. J Clin Oncol 1983; 1: 179-83
41. Johnson DH, Hainsworth JD, Linde RB, et al. Testicular function following combination chemotherapy with cis-platin, vinblastine, and bleomycin. Med Pediatr Oncol 1984; 12: 233-8
42. Leitner SP, Bosl GJ, Bajorunas D. Gonadal dysfunction in patients treated for metastatic germ-cell tumors. J Clin Oncol 1986; 4: 1500-5
43. Nijman JM, Schraffordt Koops H, Sleijfer DT. Gonadal function after surgery and chemotherapy in men with stage II and III nonseminomatous testicular tumors. J Clin Oncol 1987; 5: 651-6
44. Hansen PV, Trykker H, Helkjaer PE, et al. Testicular function in patients with testicular cancer treated with orchiectomy alone or orchiectomy plus cisplatin-based chemotherapy. J Natl Cancer Inst 1989; 81: 1246-50
45. Hansen SW, Berthelsen JG, von der Maase H. Long-term fertility and Leydig cell function in patients treated for germ cell cancer with cisplatin, vinblastine, and bleomycin versus surveillance. J Clin Oncol 1990; 8: 1695-8
46. Stuart NSA, Woodroffe CM, Grundy R, et al. Long-term toxicity of chemotherapy for testicular cancer – the cost of cure. Br J Cancer 1990; 61: 479-84
47. Bissett D, Kunkeler L, Zwanenburg L, et al. Long-term sequelae of treatment for testicular germ cell tumours. Br J Cancer 1990; 62: 655-9
48. Petersen PM, Hansen SW, Giwercman A, et al. Dose-dependent impairment of testicular function in patients treated with cisplatin-based chemotherapy for germ cell cancer. Ann Oncol 1994; 5: 355-8
49. Bokemeyer C, Berger CC, Kuczyk MA, et al. Evaluation of long-term toxicity after chemotherapy for testicular cancer. J Clin Oncol 1996; 14: 2923-32
50. Carroll PR, Whitmore WF, Herr HW. Endocrine and exocrine profiles of men with testicular tumors before orchiectomy. J Urol 1987; 137: 420-3
51. Petersen PM, Giwercman A, Skakkebaek NE, et al. Gonadal function in men with testicular cancer. Semin Oncol 1998; 25: 224-33
52. Horwich A, Nicholls EJ, Hendry WF. Seminal analysis after orchiectomy in stage I teratoma. Br J Urol 1988; 62: 79-83
53. Hansen PV, Trykker H, Andersen J, et al. Germ cell function and hormonal status in patients with testicular cancer. Cancer 1989; 64: 956-61
54. Fossa SD, Aass N, Molne K. Is routine pre-treatment cryopreservation of semen worthwhile in the management of patients with testicular cancer? Br J Urol 1989; 64: 524-9
55. Aass N, Fossa SD, Theodorsen L, et al. Prediction of long term gonadal toxicity after standard treatment for testicular cancer. Eur J Cancer 1991; 27: 1087-91
56. Fossa SD, Silde J, Theodorsen L, et al. Pre-treatment DNA ploidy of sperm cells as a predictive parameter of post-treatment spermatogenesis in patients with testicular cancer. Br J Urol 1994; 74: 359-65
57. Lampe H, Horwich A, Norman A, et al. Fertility after chemotherapy for testicular germ cell cancers. J Clin Oncol 1997; 15: 239-45
58. Hartlapp JM, Brensing KM, Voss R, et al. Long-term impairments of the gonadal function after cisplatin-based chemotherapy in 140 patients with testicular cancer [abstract]. Proc Am Soc Clin Oncol 1990; 9: 133
59. Dearnaley DP, Horwich A, Hern R, et al. Combination chemotherapy with bleomycin, etoposide, and cisplatin (BEP) for metastatic testicular teratoma: long term follow-up. Eur J Cancer 1991; 27: 684-91
60. Aass N, Fossa SD. Late side effects in patients treated for testicular cancer. Adv Biosci 1994; 91: 337-43
61. Brennemann W, Stoffel-Wagner B, Helmers A, et al. Gonadal function of patients treated with cisplatin based chemotherapy for germ cell cancer. J Urol 1997; 158: 844-50
62. Pont J, Albrecht W. Fertility following chemotherapy for testicular germ cell cancer. In: Jones WG, Appleyard I, Harnden P, et al., editors. Germ cell tumours IV. London: John Libbey & Co. Ltd, 1998: 389-94
63. Senturia YD, Peckham CS. Children fathered by men treated for testicular cancer. Eur J Cancer 1990; 26: 429-32
64. Hansen PV, Glavind K, Panduro J, et al. Paternity in patients with testicular germ cell cancer: pretreatment and post-treatment findings. Eur J Cancer 1991; 27: 1385-9
65. Kleinerman RA, Lieberman JV, Li FP. Second cancer following cancer of the male genital system in Connecticut, 1935-1982. NCI Monogr 1985; 68: 139-47
66. Coleman MP, Bell CMJ, Fraser P. Second primary malignancy after Hodgkin's disease, ovarian cancer and cancer of the testis. A population-based cohort study. Br J Cancer 1987; 56: 349-55
67. Kaldor JM, Day NE, Band P, et al. Second malignancies following testicular cancer, ovarian cancer and Hodgkin's disease. An international collaborative study among cancer registries. Int J Cancer 1987; 39: 571-85
68. Bokemeyer C, Schmoll HJ. Secondary neoplasms following treatment of malignant germ cell tumors. J Clin Oncol 1993; 11: 1703-9
69. Moeller H, Mellemgaard A, Jacobsen GK, et al. Incidence of second primary cancer following testicular cancer. Eur J Cancer 1993; 29 : 672-6
70. van Leeuwen FE, Stiggelbout AM, van der Belt-Dusebaut AW, et al. Second cancer risk following treatment of malignant germ cell tumors. J Clin Oncol 1993; 11: 415-24
71. Bokemeyer C, Schmoll HJ. Treatment of testicular cancer and the development of secondary malignancies. J Clin Oncol 1995; 13: 283-92
72. Nichols CR, Roth BJ, Heerema N, et al. Hematologic neoplasia associated with primary mediastinal germ-cell tumors. N Engl J Med 1990; 322: 1425-9
73. Fizazi K, Culine S, Droz JP, et al. Primary mediastinal nonseminomatous germ cell tumors: results of modern therapy including cisplatin-based chemotherapy. J Clin Oncol 1998; 16: 725-32
74. Ratain MJ, Rowley JD. Therapy-related acute myeloid leukemia secondary to inhibitors of topoisomerase II: from the bedside to the target genes. Ann Oncol 1992; 3: 107-11
75. Pedersen-Bjergaard J, Daugaard G, Hansen SW, et al. Increased risk of myelodysplasia and leukemia after etoposide, cisplatin and bleomycin for germ cell tumors. Lancet 1991; 338: 1269-70
76. Bajorin DF, Motzer RJ, Rodriguez E, et al. Acute nonlymphocytic leukemia in germ cell tumor patients treated with etoposide-containing chemotherapy. J Natl Cancer Inst 1993; 85: 60-2
77. Nichols CR, Breeden ES, Loehrer PJ, et al. Secondary leukemia associated with a conventional dose of etoposide: review a serial germ cell tumor protocols. J Natl Cancer Inst 1993; 85: 36-40
78. Boshoff C, Begent RHJ, Oliver RTD, et al. Secondary tumours following etoposide containing therapy for germ cell cancer. Ann Oncol 1995; 6: 35-40

79. Roth BJ, Greist A, Kubilis PS, et al. Cisplatin-based combination chemotherapy for disseminated germ cell tumors: long-term follow-up. J Clin Oncol 1988; 6: 1239-47
80. Stoter G, Koopman A, Vendrick CPJ, et al. Ten-year survival and late sequelae in testicular cancer patients treated with cisplatin, vinblastine, and bleomycin. J Clin Oncol 1989; 7: 1099-104
81. Hansen SW, Helweg-Larsen S, Trojaborg W. Long-term neurotoxicity in patients treated with cisplatin, vinblastine, and bleomycin for metastatic germ cell cancer. J Clin Oncol 1989; 7: 1457-61
82. Boyer M, Raghavan D, Harris PJ, et al. Lack of late toxicity in patients treated with cisplatin-containing combination chemotherapy for metastatic testicular cancer. J Clin Oncol 1990; 8: 21-6
83. Aass N, Kaasa S, Lund E, et al. Long-term somatic side-effects and morbidity in testicular cancer patients. Br J Cancer 1990; 61: 151-5
84. Bokemeyer C, Frank B, Van Rhee J, et al. Peripheral neuropathy following cancer chemotherapy. Long-term results in patients with curable neoplasms. Tumordiagn Ther 1993; 14: 232-7
85. Pollera CF, Marolla P, Nardi M, et al. Very high-dose cisplatin-induced ototoxicity: a preliminary report on early and long-term effects. Cancer Chemother Pharmacol 1988; 21: 61-4
86. Stuart NSA, Grundy R, Woodroffe CM, et al. Quality of life after treatment for testicular cancer. The patient's view. Eur J Cancer 1990; 26: 291-4
87. Adoue D, Arlet P. Bleomycin and Raynaud's phenomenon. Ann Intern Med 1984; 100: 770
88. Teutsch C, Lipton A, Harvey HA. Raynaud's phenomenon as a side effect of chemotherapy with vinblastine and bleomycin for testicular carcinoma. Cancer Treat Rep 1977; 61: 925-6
89. Vogelzang NJ, Torkelson JL, Kennedy BJ. Hypomagnesemia, renal dysfunction, and Raynaud's phenomenon in patients treated with cisplatin, vinblastine, and bleomycin. Cancer 1985; 56: 2765-70
90. Hansen SW, Olsen N. Raynaud's phenomenon in patients treated with cisplatin, vinblastine, and bleomycin for germ cell cancer: measurement of vasoconstrictor response to cold. J Clin Oncol 1989; 7: 940-2
91. Vogelzang NJ, Frenning DH, Kennedy BJ. Coronary artery disease after bleomycin and vinblastine. Cancer Treat Rep 1980; 64: 1159-60
92. Nichols CR, Roth BJ, Williams SD, et al. No evidence of acute cardiovascular complications of chemotherapy for testicular cancer: an analysis of the Testicular Cancer Intergroup study. J Clin Oncol 1992; 10: 760-5
93. Gietema JA, Sleijfer DT, Willemse PHB, et al. Long-term follow-up of cardiovascular risk factors in patients given chemotherapy for disseminated nonseminomatous testicular cancer. Ann Intern Med 1992; 116: 709-15
94. Raghavan D, Cox K, Childs A, et al. Hypercholesterolemia after chemotherapy for testis cancer. J Clin Oncol 1992; 10: 1386-9
95. Pont J, Albrecht W, Postner G, et al. Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. J Clin Oncol 1996; 14: 441-8
96. Cullen MH, Stenning SP, Parkinson MC, et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. J Clin Oncol 1996; 14: 1106-13

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