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Diagnosis and Treatment of Patients with Testicular Germ Cell Cancer

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Abstract

Testicular germ cell tumours are a highly curable malignancy even in the presence of metastases, with an overall survival rate of approximately 90 to 95% when all stages are considered. Current therapeutic strategies aim at risk-adapted therapy, trying to maintain favourable overall results while reducing treatment-related toxicity, particularly in non-advanced disease.

In stage I disease, unilateral inguinal orchiectomy represents the standard diagnostic and therapeutic approach. For patients with clinical stage I seminoma, prophylactic para-aortic radiotherapy with 26Gy is commonly employed. In pa-

tients with nonseminomatous germ cell tumours (NSGCT) at clinical stage I, the 3 options are: (i) retroperitoneal lymphadenectomy; (ii) a wait-and-see strategy; or (iii) 2 cycles of adjuvant chemotherapy. The individual risk profile for tumour recurrence, mainly based on histopathological criteria such as vascular tumour invasion, should guide treatment decisions in this group of patients.

Radiotherapy is still the standard approach in clinical stage IIA/B seminoma, whereas in patients with a low tumour burden of NSGCT, retroperitoneal lymphadenectomy is frequently used followed by surveillance or adjuvant chemotherapy. Primary chemotherapy in these stages of disease may be at least equally successful.

Major progress has also been achieved in the treatment of NSGCT patients with metastatic disease greater than clinical stage IIB, for whom primary chemotherapy represents the standard approach. After cisplatin-based combination chemotherapy, between 70 and 90% of patients will achieve a durable remission. In patients with 'good risk' metastatic disease, 3 cycles of cisplatin, etoposide and bleomycin (PEB) remain the standard treatment, despite several randomised trials trying to avoid the lung-toxic bleomycin or substituting cisplatin by carboplatin. In patients with 'intermediate' and 'poor prognosis' disease, 4 cycles of PEB given at 3-week intervals are considered routine treatment.

The role of high dose chemotherapy with peripheral autologous blood stem cell transplantation is currently being investigated for patients presenting initially with advanced (poor prognosis) metastatic disease and for patients with relapse after previous chemotherapy, in whom conventional-dose salvage regimens will only result in 20% long-term survival.

Because of the large group of patients with metastatic disease being cured, the possible long-term adverse effects of treatment have become important. Only a slightly elevated risk for therapy-related secondary malignancies has been identified. Long-term adverse effects associated with cisplatin may affect a larger proportion of patients. Further research should focus on reducing the risk of chemotherapy-related chronic toxicity.

Testicular cancer is the most common solid tumour in men aged between 20 and 35 years. An incidence rate of 6 to 8 per 100 000 was observed in the Western world.[1] Overall, the incidence of testicular cancer has more than doubled in the past 40 years.[2,3] Despite some hypotheses, the cause of testicular cancer remains unknown. Cryptorchidism is the best established factor predisposing to the disease, with a combined relative risk of 5.3 [95% confidence interval (CI) 4.1 to 6.9] from 9 case-control studies.[4] Only weak and inconsistent estimates have been found for other aetiologically relevant factors such as inborn inguinal hernia.[5] Mediastinal germ cell tumours appear to be associated with Klinefelter's syndrome and with Down's syndrome.[6] Genetic factors seems to influence the occurrence of testicular cancer. A family history has been encountered in 1.35% of patients summarised from 11 literature reports. The risk for first-degree relatives of patients with the disease is 3- to 10-fold increased.[7]

The typical clinical presentation of a primary testicular tumour is a painless testicular mass. An intratesticular hypoechoic lesion, frequently with diffuse microcalcifications in cases of seminoma, is seen on ultrasound examination.

A radical inguinal orchiectomy is the only acceptable procedure minimising local tumour recurrence and lymphatic spread, and should be performed in all patients with unilateral cancer. Primary extragonadal germ cell tumours comprise fewer than 10% of all cases. The mediastinum and

the retroperitoneum are the most common sites. In principle, the management of extragonadal and testicular germ cell cancer is the same with respect to the type of chemotherapy used in metastatic disease. The primary site is an independent factor in current staging and risk classifications.

1. Histology and Aetiology

For the histopathological classification of testicular cancer the World Health Organization (WHO) classification is commonly used.[8] In terms of clinical management, testicular germ cell tumour is divided into 2 major subgroups, seminoma and nonseminoma, each accounting approximately for half of testicular cancer cases.

Seminoma frequently appears in the fourth decade of life. Occasionally seminomas contain trophoblastic giant cells capable of producing human chorionic gonadotropin (hCG). Spermatocytic seminoma is a rare histological variant seen mostly in men older than the age of 45 years, with a minimal metastatic potential.

Nonseminomatous germ cell tumours (NSGCT) – embryonal carcinoma, choriocarcinoma, yolk sac tumour and teratoma – present most frequently in the third decade of life. Most NSGCT are mixed, consisting of 2 or more histological subtypes. Even when seminoma is a component of the tumour, the presence of any nonseminomatous elements classifies the tumour as NSGCT with respect to the clinical management. Teratoma refers to germ cell tumours containing all 3 germ layers with varying degrees of differentiation. These terminally differentiated tumours are technically not malignant; however, metastases have been reported and death may result from slowly progressive, unresectable local disease. Nevertheless, the most appropriate therapeutic option is complete surgical intervention, because differentiated teratomas are not responsive to chemotherapy.

Intratubular germ cell neoplasia (carcinoma *in situ*; CIS)[9] is generally accepted as the precursor lesion of invasive testicular cancer in the adult, both for seminoma as well as for NSGCT. Increased incidences of CIS (2 to 5%) are found both in cryptorchid testes and in the contralateral testis in patients with a documented prior testicular cancer,[10] while in men with impaired fertility the incidence is about 0.5%.[11]

Cytogenetic examinations show that male testicular cancer cells are nearly always hyperdiploid, frequently triploid or tetraploid, and have at least one X and one Y chromosome.[12] An isochromosome of the short arm of chromosome 12 [i(12p)] is a marker chromosome identified in all histological subtypes arising from all primary sites[13] and in about 80% of testicular cancers that grow in culture.[14,15] It has also been identified in cells of CIS.[16] These findings may be evidence that one or more genes on the short arm of chromosome 12 are critical to malignant transformation. In the absence of i(12p) in some karyotypically abnormal germ cell tumours, aberrantly banded marker chromosomes composed of multiple copies of 12p have often been identified. Therefore, excess 12p copy number can be demonstrated in essentially all germ cell tumours, including those that are i(12p)-negative. Characteristic deletions on 12q have also been observed, suggesting that a tumour suppressor gene might be present on the long arm of chromosome 12, which may undergo allelic loss during malignant transformation.[13] These findings form the basis for a hypothesis of malignant transformation of primordial germ cells: meiotic spermatocytes that have undergone crossing over and in which DNA repair is unsuccessful should undergo apoptosis. However, because of excess 12p gene copy numbers and expression, and additional mutational genetic events involving cell cycle control genes, the cells undergo 'rescue' and enter mitosis. The rescued transformed cells are XY, have a 2C or more chromosome number, have the potential for widespread gene loss through genomic instability, and display increased 12p copy number.

Immunohistochemical markers, including human placental alkaline phosphatase for seminoma or embryonal carcinoma, the tumour marker α-fetoprotein (AFP), hCG and also low molecular weight keratins in NSGCT, may be useful in establishing a diagnosis of a germ cell tumours in cancer

Table I. Tumour node metastasis (TNM) staging classification of testicular cancer[19]

Primary tumour (pT)	
pTX	Primary tumour cannot be assessed (if no radical orchiectomy has been performed, TX is used)
pT0	No evidence of primary tumour (e.g. histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)
pT1	Tumour limited to the testis and epididymis without vascular/lymphatic invasion; tumour may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumour limited to the testis and epididymis with vascular/lymphatic invasion, or tumour extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumour invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades the scrotum with or without vascular/lymphatic invasion
Regional lymph nodes (N)	
Clinical involvement	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2cm or less in greatest dimension; or multiple lymph nodes, none more than 2cm in greatest dimension
N2	Metastasis with a lymph node mass, more than 2cm but not more than 5cm in greatest dimension; or multiple lymph nodes, any 1 mass greater than 2cm but not more than 5cm in greatest dimension
N3	Metastasis with lymph node mass more than 5cm in greatest dimension
Pathological involvement (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass, 2cm or less in greatest dimension and less than or equal to 5 nodes positive, none more than 2cm in greatest dimension
pN2	Metastasis with a lymph node mass, more than 2cm but not more than 5cm in greatest dimension; or more than 5 nodes positive, none more than 5cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass more than 5cm in greatest dimension
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Distant metastasis other than to nonregional lymph nodes and lungs
Serum tumour markers (S)	
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 × N and hCG (IU/L) <5000 and AFP (ng/ml) <1000
S2	LDH 1.5-10 × N or hCG (IU/L) 5000-50 000 or AFP (ng/ml) 1000-10 000
S3	LDH >10 × N or hCG (IU/L) >50 000 or AFP (ng/ml) >10 000

AFP = α-fetoprotein; **hCG** = human chorionic gonadotropin; **LDH** = lactate dehydrogenase.

of uncertain histogenesis.[17] The presence of i(12p) may be further evidence of the germ cell tumour relationship of tumours of unknown origin.

2. Staging and Classification

Multiple staging systems are in use to classify and subsequently manage patients with testicular cancer. According to the Workshop for Staging and Treatment of Testicular Cancer, Lugano 1979, stage I disease is confined to the testis, stage II disease is restricted to retroperitoneal lymph nodes, and stage III disease is located at supradiaphragmatic or other nodal sites, or includes visceral disease.[18] The different prognostic classifications used for clinical trials of chemotherapy in patients

with advanced disease, encompassing bulky retroperitoneal or supradiaphragmatic nodal disease and visceral metastases, have varied considerably.

The classification of the Union International contre le Cancer (UICC) classification, updated in 1997, includes the categories T (primary tumour), N (regional lymph nodes), M (distant metastases) and S [elevation of the tumour markers lactate dehydrogenase (LDH), hCG and AFP] after clinical (c) or pathological (p) staging. As well as incorporating nonanatomical prognostic information, such as tumour marker elevations (category S), this new Tumour Node Metastasis (TNM) staging classification system (tables I and II) includes a new definition of T2 stage which includes lymphatic/vascular invasion (see section 3) and distinguishes between pulmonary (M1a) and nonpulmonary (M1b) visceral metastases.[19] These modifications are partially based on the results of the new International Germ Cell Cancer Consensus Group (IGCCCG) classification for metastatic disease (table III), which has been widely accepted since its introduction in 1995.[20]

To define the extent of disease and to determine the appropriate treatment, staging should include pathological examination of the primary tumour, physical examination, determination of serum concentrations of AFP, hCG and LDH, and radiographic studies such as plain chest radiograph and computed tomography (CT) scans of abdomen and chest. In patients with advanced metastatic disease (poor prognosis), bone scans and CT scans of the brain are recommended as additional initial staging investigations, especially in patients with a histology of choriocarcinoma.

Table II. Stage grouping of testicular cancer.[19] This stage grouping uses the classification shown in table I

Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
Stage IIB	Any pT/TX	N2	M0	S0
Stage IIC	Any pT/TX	N3	M0	S0
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

3. Treatment of Clinical Stage I Disease

3.1 Seminoma

The management of clinical stage I seminoma has changed little over the last 20 years. Radiation therapy with conventional fractionation to a total dose of 25 to 30Gy has become the standard treatment. Lower doses of radiotherapy are under investigation. Radiation fields have been limited to para-aortic nodes in recent years. The relapse rate within the irradiated portal after adequate radiation therapy is negligible. The rate of systemic relapse, which usually presents as a supraclavicular mass, ranges from 2 to 9% and the mortality is under 2%.[21,22] Although the dose of radiation therapy is low and cure rates are high, long term sequelae include the potential for an increased incidence of gastrointestinal neoplasms.[23]

The 5-year relapse rate after observation alone without adjunctive radiotherapy is approximately 15 to 20%. A retrospective study of 549 patients obtained from 3 major centres in Canada, Denmark and the UK identified tumour size (>4cm) and invasion of the rete testis as important predictors of outcome. Both were associated with a nearly 2-fold higher relative risk for relapse in clinical stage I seminoma.[24] Because of the need for prolonged intensive follow-up of patients and the previous lack of sufficient predictors for relapse, a policy of surveillance was not widely used in Europe.

Because of the chemosensitivity of seminoma, single-agent carboplatin is currently being investigated as an alternative to radiation therapy in clinical stage I. This agent was found to possess efficacy in advanced disease combined with low

toxicity. In Germany a randomised trial comparing adjuvant para-aortal radiotherapy (26Gy) with 2 cycles of carboplatin chemotherapy is ongoing and more than 350 patients had been randomised by 1998.

3.2 Nonseminomatous Germ Cell Tumours (NSGCT)

Patients with nonseminomatous testicular cancer at clinical stage I will have a long-term survival rate of approximately 98%. Three options are currently being discussed.

3.2.1 Retroperitoneal Lymphadenectomy

The main advantage of retroperitoneal lymphadenectomy (RLA), still considered the gold standard for stage I NSGCT, is the achievement of an exact pathological staging.[25] RLA detects false-negative clinical staging with pathologically confirmed stage II disease in approximately 20%, and false-positive clinical staging, preoperatively classified as clinical stage IIA/B but with pathological stage I disease, in approximately 10%. These latter patients might have had to undergo unnecessary chemotherapy if no RLA had been performed. On the other hand, when RLA is not performed, there is a 20 to 30% risk that patients with clinical stage I disease will develop tumour progression on a wait-and-see programme. The disadvantages of RLA are that, even with modified techniques, the operation may result in a considerable morbidity rate of 11 to 23% and in a mortality rate of approximately 0.3%.[26] Despite a previous RLA, tumour recurrences in the retroperitoneum ranged from 2 to 10% and distant metastases occurred in 7 to 12% of patients after 2 years.[27-30]

Nerve-sparing operation techniques, based on several meticulous mapping studies of retroperitoneal node involvement in early stage disease,[31,32] require avoidance of sympathetic fibres of the hypogastric plexus anterior to the aortic bifurcation or prospective identification of postganglionic nerves and their preservation before lymphadenectomy, as described by Donohue et al.[33] These techniques may result in a 100% antegrade function, few retroperitoneal relapses and a >99% cure rate in an experienced centre.[28] Since retrograde ejaculation remains a potential risk with any retroperitoneal lymph node dissection (RPLND) where prospective identification of postganglionic nerves is not specifically performed, preoperative sperm banking is recommended.

Table III. International Germ Cell Cancer Collaborative Group classification of testicular cancer[20]

Good prognosis	
Nonseminoma	Testis/retroperitoneal primary, good markers[a] and no nonpulmonary visceral metastases
Seminoma	Any primary site, any markers and no nonpulmonary visceral metastases
Intermediate prognosis	
Nonseminoma	Testis/retroperitoneal primary, intermediate markers[b] and no nonpulmonary visceral metastases
Seminoma	Any primary site, any markers and nonpulmonary visceral metastases
Poor prognosis	
Nonseminoma	Mediastinal primary site or testis/retroperitoneal with either nonpulmonary visceral metastases *or* poor markers[c]

a Good markers: AFP <1000 ng/ml and hCG <1000 ng/mg (approx. 5000 IU/L) and LDH <1.5 × N.

b Intermediate markers: AFP <1000-10 000 ng/ml or hCG <1000-10 000 ng/mg (approx. 5000-50 000 IU/L) or LDH <1.5-10 × N.

c Poor markers: AFP >10 000 ng/ml or hCG >10 000 ng/mg (approx. 50 000 IU/L) or LDH >10 × N.

AFP = α-fetoprotein; **hCG** = human chorionic gonadotropin; **LDH** = lactate dehydrogenase; **N** = upper limit of normal for the LDH assay.

3.2.2 Wait-and-See Strategy

In view of the morbidity rate of RLA and the high cure rates with chemotherapy in patients with metastatic spread, the so-called surveillance or wait-and-see strategy was initiated as an alternative to the routine use of RLA.[34] During multiple surveillance studies which have been initiated by several centres, a median tumour progression rate of 28% after orchiectomy alone was observed. Therefore, a wait-and-see strategy can only be performed when sufficient diagnostic skill and equipment is offered and when patients' compliance is guaranteed. After tumour progression and treat-

ment by systemic chemotherapy, between 14 and 32% of patients will require a surgical resection of residual tumour masses, but the survival rate will still be about 98%.

3.2.3 Adjuvant Chemotherapy

The main advantage of primary adjuvant chemotherapy is that the rate of tumour recurrences is reduced to ≤5%. The risk of secondary malignancies or secondary leukaemia following chemotherapy seems to be very low.[35] However, as with the use of routine primary RLA, approximately 70% of patients will undergo an unnecessary treatment if chemotherapy is applied without adequate selection of patients at high risk for progression.

3.2.4 Factors of Tumour Recurrence Guiding Treatment Decisions

The identification of the individual risk profile of clinical stage I nonseminoma for tumour recurrence will allow a risk-adapted therapeutic strategy: wait-and-see for patients at 'low' risk for metastatic disease and RLA (or adjuvant chemotherapy in clinical trials) for those at 'high' risk. A prospective study (including 259 patients) and a retrospective study (including 373 patients) performed by the UK Medical Research Council[36] identified the histological characteristics of the primary germ cell tumour that determine the individual risk:

- infiltration of testicular veins (the most important factor)
- infiltration of lymphatic vessels
- absence of yolk sac elements
- presence of embryonal carcinoma.

Based on these factors in the primary testicular tumour specimen, the Freedman score can be calculated, which has significant predictive value for the occurrence of tumour progression. A follow-up study in 250 patients of the Intergroup trial identified intravenous invasion as highly predictive for relapse in pathological stage I (6.0 *vs* 19.4%).[30]

In a recent prospective study,[37] high-risk patients according to the Freedman score received 2 cycles of adjuvant chemotherapy with cisplatin, etoposide and bleomycin (PEB). The low tumour progression rate of 2% demonstrates that adjuvant primary chemotherapy may represent a successful risk-adapted strategy based on established histological tumour characteristics. No significant long-term toxicity appears to be associated with this regimen.[38]

As well as these histological factors, other tumour characteristics are currently under investigation to determine their prognostic potential. These include biological factors [DNA index, proliferation index (using the monoclonal antibody MIB-1, which stains cells in the proliferating phase of the cell cycle), S-phase fraction] and molecular factors [i(12p), amplifications of *ras* oncogene, *hst*-1, stem cell factor receptor ligand, altered c-*kit* expression and alterations of p53].[39,40] By combining immunohistochemical (MIB-1), histopathological (volume of embryonal carcinoma) and radiological parameters, patients with an extremely low risk for metastases can be identified and consequently offered surveillance.[41]

3.3 Clinical Stage IS

TNM classification clinical stage IS, persistent serum tumour marker elevation after orchiectomy without radiological evidence of disseminated disease, is generally an indication for chemotherapy since it indicates occult metastatic disease.

4. Treatment of Clinical Stage IIA/B Disease

4.1 Seminoma

Low tumour burden clinical stage IIA/B seminoma includes patients with retroperitoneal lymph node metastases measuring less than 5cm in maximum transverse diameter. Radiation therapy is the treatment of choice for most patients with clinical stage IIA/B. The radiation portal includes the paraaortic and ipsilateral iliacic lymph nodes, and a dose of 30Gy for stage IIA and 36Gy for stage IIB seems to be adequate treatment.[42] The 2-year relapse rates were 0 and 13%, respectively, and death from seminoma is rare. Prophylactic radiation of the mediastinum or supraclavicular nodes is unnecessary.

4.2 NSGCT

In low tumour burden NSGCT, clinical stage IIA/B, RLA has been the standard approach and may be indicated in case of ipsilateral solitary lymph nodes less than 3cm. The aim of RLA is to perform a definitive therapeutic operation to reduce the risk of infield recurrences to a minimum. However, if possible and depending on the location of disease, a nerve-sparing dissection should be preferred. Lymph nodes between 3 and 5cm, even if solitary, may be associated with more extensive disease than previously detected on abdominal CT scans.

The clinical presentation of tumour-related back pain, suprahilar or retrocrural lymphadenopathy, bilateral retroperitoneal nodal metastases, or contralateral lymph nodes (even if the ipsilateral lymph nodes do not appear to be involved) generally implies unresectable disease (e.g. tumour-associated back pain) or a high likelihood of further metastases (suprahilar and retrocrural adenopathy). In these patients, initial chemotherapy (3 cycles of PEB) is preferred, and results in a complete remission rate of 60 to 70%; approximately 30% of patients have to undergo secondary surgery for residual tumour masses.

The routine application of adjuvant chemotherapy after RLA in resected pathological stage IIA/B disease appears to be necessary for patients with a high risk of relapse, defined as more than 6 involved lymph nodes, any lymph nodes of size greater than 2cm or extranodal extension. Adjuvant treatment programmes with 2 cycles of PEB or, as demonstrated in a recent study, 2 cycles of PE (i.e. PEB without bleomycin) result in a 98% relapse-free survival.[43] Patient compliance, psychological factors and age may limit the use of adjuvant chemotherapy. A randomised trial comparing observation followed by standard treatment in case of relapse versus 2 cycles of adjuvant chemotherapy after surgery has demonstrated equivalent survival rates in both arms.[44] However, it should be emphasised that this Intergroup trial had limited statistical power to detect a small survival difference: 3 patients died in the observation and 1 in the treatment arm.

Flow cytometric or cytophotometric DNA analysis did not identify prognostic factors predicting the risk for subsequent tumour recurrence in patients with pathological stage IIA/B disease,[45] but careful pathological scrutiny provides important prognostic information in these patients. As with pathological stage I, intravenous invasion of lymph nodes appears to be predictive for relapse after RLA in pathological stage II disease (24.0 *vs* 63.5%, n = 88).[30]

5. Treatment of Clinical Stage IIC/D or III (Advanced) Seminoma

Patients with greater than stage IIB seminoma have a high relapse rate (approximately 20 to 30%) with radiation therapy alone.[46,47] Therefore, chemotherapy is preferred, resulting in complete response rates of approximately 80 to 90% with either standard cisplatin, or 77 to 93% using carboplatin-based combination chemotherapy. Single-agent carboplatin chemotherapy yields disease-free survival rates of approximately 75% (table IV).[48-59]

Two randomised trials have compared the 2 platin analogues. 69 cases of seminoma with 'good risk' disease [according to the Memorial Sloan Kettering Cancer Center (MSKCC) classification[60]] received either PE or carboplatin plus etoposide (CE). Whereas initial response to treatment was 87% for PE and 94% for CE, decreased event-free survival rates in patients treated with CE (82 *vs* 87%) were observed, which was not statistically significant and may be caused by the small sample size.[61] In 1996, Horwich and colleagues[62] reported a randomised trial comparing 4 cycles of carboplatin 400 mg/m^2 with 4 cycles of cisplatin 100 mg/m^2 plus etoposide 120 mg/m^2 on days 1 to 3. This study stopped recruitment after 130 patients because of reports of the adverse results of carboplatin in nonseminoma. 2-year progression-free interval was 76 versus 82% in favour of PE. Overall survival was found to be statistically equal, perhaps because of the efficacy of cisplatin-based

Table IV. Results of carboplatin- and cisplatin-based chemotherapy in advanced seminoma

Author	Year	Regimen	No. of patients	Continuous CR rate (%)
Carboplatin				
Horwich et al.[53]	1992	C × 4-6	70	77
Schmoll et al.[51]	1993	C × 3-6	42	71
Mencel et al.[52]	1994	CE × 4	35	83
Sleijfer et al.[54]	1996	CIO	27	93
Jones et al.[55]	1997	CCyc	31	77
Cisplatin				
Pizzocaro et al.[50]	1986	PVB/PEB	31	75
Logothetis et al.[49]	1987	P/Cyc	42	92
Fossa et al.[56]	1987	PVB/PEB	54	78
Loehrer et al.[57]	1987	PVB/PEB	60	66
Mencel et al.[52]	1994	VAB-6/EP	105	87
Fossa et al.[48]	1995	PIO	42	90
Clemm et al.[58]	1995	PEI/PVI	77	92
Horwich et al.[59]	1997	PEB/PVB	45	93

B = bleomycin; **C** = carboplatin; **CR** = complete response; **Cyc** = cyclophosphamide; **E** = etoposide; **I** = ifosfamide; **O** = vincristine; **P** = cisplatin; **V** = vinblastine; **VAB-6** = cisplatin + vinblastine + dactinomycin + bleomycin + cyclophosphamide.

salvage treatment after relapse from carboplatin chemotherapy.[62]

The German Testicular Cancer Study Group (GTCSG) is currently evaluating the efficacy of 4 cycles of either single-agent carboplatin or cisplatin, etoposide and ifosfamide (PEI) in an ongoing randomised trial. More than 240 patients have been included and the final analysis is expected in mid-1999.

Outside the setting of clinical trials, the standard treatment for patients with 'good prognosis' or 'intermediate prognosis' seminoma according to the IGCCCG criteria (table III) consists of 3 or 4 cycles, respectively, of cisplatin-based chemotherapy (see section 6).

6. Treatment of Patients with Metastatic NSGCT

6.1 Good Prognosis Disease

With the success of cisplatin-based chemotherapy in testicular germ cell tumours, the aim of chemotherapy in patients with low volume metastatic disease [now designated 'good prognosis' by the IGCCCG (table III)] has been to reduce treatment-associated toxicity without compromising the long-term survival rate.[63,64]

Until the mid-1980s the standard treatment regimen for metastatic testicular cancer was the combination of cisplatin, vinblastine and bleomycin (PVB). In 1987, the South East Cancer Study Group demonstrated that 4 cycles of the PVB regimen can be replaced by 4 cycles of PEB, with etoposide being given instead of vinblastine. This resulted in higher antitumour activity in patients with advanced disease and in overall lower toxicity.[63] The same study group reported 2 years later that, for the subgroup of low-risk patients, the toxicity of the fourth treatment cycle of PEB could be avoided, since 3 cycles achieve comparable results.[65] A further randomised investigation of 3 cycles of PEB versus 3 cycles of PE with the aim of avoiding bleomycin-associated toxicity demonstrated a significantly inferior progression-free interval (86 *vs* 69%) and overall survival rate (95 *vs* 86%) for the PE arm. Altogether, 171 patients with 'minimal' and 'moderate' stage disease, according to the Indiana University classification criteria,[64] were fully assessable. The levels of toxicity were stated to be comparable.[66]

A retrospective analysis from the MSKCC of 2 earlier randomised studies using 4 cycles of PE in good prognosis patients yielded a complete remission rate of 96% and a relapse rate of 5%. These

results appear equivalent to those achieved with 3 cycles of PEB.[67] In a prospective randomised trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) comparing 4 cycles of PEB versus 4 cycles of PE in patients with a good prognosis, according to the Indiana University classification, no difference in survival or time to progression could be detected after a follow-up duration of more than 7 years. However, this result may be attributed to the low number of events in the trial. Complete response rates were in favour of PEB (95 *vs* 87%), but acute and late pulmonary toxicity, as well as neurotoxicity, were significantly greater in those patients who received bleomycin. Raynaud's phenomenon at WHO grade I to III occurred exclusively in the PEB arm (8%).[68]

In contrast with the retrospective data of the MSKCC,[67] the EORTC trial[68] demonstrated a lower efficacy of the PE arm, which may be attributed to the different etoposide dosages used. The American patients received etoposide 500 mg/m^2 per cycle, whereas in the EORTC study 360 mg/m^2 was used.

A EORTC study comparing 3 versus 4 cycles and 3-day versus 5-day schedules of the PEB regimen in good prognosis patients has recently completed recruitment and awaits analysis.

Replacement of the nephrotoxic and neurotoxic drug cisplatin by its less toxic derivative carboplatin[69,70] results in an approximately 10% lower relapse-free survival and a slightly but significantly reduced overall survival rate. The largest study, conducted by the EORTC and the Medical Research Council, recruited 598 patients. This trial revealed a significantly inferior failure-free survival rate at 1 year of 77 versus 91%, and a 3-year overall survival rate of 90 versus 97%, for carboplatin, etoposide and bleomycin (CEB) as compared with PEB. In this trial, the bleomycin dosage was reduced from the standard 90 mg/cycle to only 30mg/cycle in both treatment arms.[56]

These randomised investigations in good risk testicular cancer are summarised in table V.[61,65,66,68-71] Carboplatin is not a fully equivalent substitute for cisplatin in standard-dose therapy of metastatic NSGCT. This is consistent with results achieved in xenograft animal models,[72] which achieved equivalent cytotoxic activity when carboplatin was used at 6- to 10-fold higher doses than cisplatin.

6.2 Intermediate Prognosis Disease

The optimal treatment for patients with intermediate prognosis germ cell cancer is difficult to define, since this subgroup was only recently defined

Table V. Randomised trials in good prognosis metastatic testicular cancer (adapted from Bosl et al.,[58])

Reference	Classification	Regimens	Aim of the trial	CR rate (%)	Durable CR rate (%)	Conclusion
Saxman et al.[65]	Indiana	PEB × 4	Reduction of treatment cycles	97	88	Equivalent
		PEB × 3		98	87	
Bosl et al.[71]	MSKCC	VAB-6 × 3	Introduce new 2-drug regimen	96	85	Equivalent
		PE × 4		93	82	
de Wit et al.[68]	EORTC	PEB × 4	Avoid bleomycin	95	91	PE × 4 was
		PE × 4		87	83	inferior
Loehrer et al.[66]	Indiana	PEB × 3	Avoid bleomycin	94	86	PE × 3 was
		PE × 3		88	69	inferior
Bajorin et al.[61]	MSKCC	PE × 4	Carboplatin *vs* cisplatin	80	87	CE × 4 was
		CE × 4		88	76	inferior
Horwich et al.[69]	MRC/EORTC	CEB × 4	Carboplatin *vs* cisplatin	87	77	CEB × 4 was
		PEB × 4		94	91	inferior
Bokemeyer et al.[70]	Indiana	CEB × 4	Carboplatin *vs* cisplatin	96	68	CEB × 4 was
		PEB × 3		97	86	inferior

B = bleomycin; **C** = carboplatin; **CR** = complete response; **E** = etoposide; **EORTC** = European Organization for Research and Treatment of Cancer; **MRC** = Medical Research Council; **MSKCC** = Memorial Sloan Kettering Cancer Center; **P** = cisplatin; **VAB-6** = cisplatin + vinblastine + dactinomycin + bleomycin + cyclophosphamide.

Table VI. Randomised trials in poor prognosis metastatic testicular cancer (adapted from Bosl et al.[58] and Nichols et al.[67])

Reference	Classification	Regimens	Aim of the trial	CR rate (%)	Conclusion
Williams et al.[63]	Indiana	PVB × 4	Etoposide instead of vinblastine	38	PVB was inferior
		PEB × 4		63	
Wozniak et al.[79]	SWOG	PVB × 4	Etoposide instead of bleomycin	77	Equal
		PEV × 4		73	
Ozols et al.[80]	NCI	PVB × 4	Addition of etoposide plus doubled	67	PVB was inferior
		$P_{(200)}$EBV × 4	dose of cisplatin	88	
Nichols et al.[78]	Indiana	PEB × 4	Doubled dose of cisplatin	73	Equal
		$P_{(200)}$EB × 4		68	
de Wit et al.[76]	EORTC	PEB × 4	Alternating regimen	72	Equal
		PVB/PEB × 2		76	
Nichols et al.[77]	Indiana	PEB × 4	Ifosfamide instead of bleomycin	60	Equal
		PEI × 4		63	
Kaye et al.[75]	MRC/EORTC	PEB × 6	Sequential alternating regimen	57	Equal
		BOP/VIP-B × 3		54	

B = bleomycin; **C** = carboplatin; **CR** = complete response; **E** = etoposide; **EORTC** = European Organization for Research and Treatment of Cancer; **I** = ifosfamide; **MRC** = Medical Research Council; **NCI** = National Cancer Institute; **O** = vincristine; **P** = cisplatin; **SWOG** = Southwestern Oncology Group; **V** = vinblastine.

by the meta-analysis of the IGCCC study group.[20] A randomised trial compared PEB with PEI in patients with intermediate prognosis defined as any of the following: (i) lymph node metastases 5 to 10cm in diameter; (ii) lung metastases >4 in number or >3cm; (iii) hCG 5000 to 50 000 IU/L; or (iv) AFP >1000 IU/L.[73] This group of patients achieved an 83% long-term survival rate after 4 cycles of PEB, and standard dose ifosfamide was not superior to the use of bleomycin.

Possible strategies that might be tested to further improve the outcome are either to initially treat these patients with high dose chemotherapy, as investigated in poor prognosis patients, or to evaluate the role of new active drugs given in addition to the standard PEB regimen. This latter approach has been investigated in a phase I trial at the Daniel den Hoed Cancer Center, Rotterdam, The Netherlands, combining PEB with paclitaxel.[74] A randomised EORTC study comparing 4 cycles of PEB with or without paclitaxel has recently been initiated.

6.3 Poor Prognosis Disease

Despite the overall success of cisplatin-based chemotherapy in the treatment of metastatic disease, the outcome of patients classified as poor prognosis cannot be stated as satisfactory. Conventional-dose chemotherapy (4 × PEB) results in an overall survival rate of only ≤50%.[20,64] Different strategies have been investigated in the past, including the use of rapidly alternating chemotherapy with combinations of cisplatin (P), vincristine (O), bleomycin (B), vinblastine (V) and etoposide (E), such as BOP/VIP-B or PVB/PEB. However, a recently published trial comparing BOP/VIP-B with PEB/EP showed no improvement in response or survival rate, but the alternating arm was associated with more toxicity.[75,76] Results of randomised trials conducted in poor prognosis patients are shown in table VI.[63,75-80]

The rationale for dose-intensive chemotherapy is based on the hypothesis of a dose-response relationship. Before the availability of peripheral autologous blood stem cell (PBSC) transplantation and recombinant haemopoietic colony-stimulating factors (CSFs), dose intensification of cisplatin was investigated, but a randomised study clearly demonstrated that a cumulative cisplatin dose of 200 mg/m^2/cycle (5 × 40 mg/m^2) did not achieve superior survival rates compared with the conventional dose (5 × 20 mg/m^2). Rather, it resulted in increased toxicity.[68] The dose escalation of other active drugs such as etoposide and ifosfamide[81-84]

and the use of high dose carboplatin instead of cisplatin has become possible through the clinical availability of CSFs and PBSC, which have reduced the duration of leuco- and thrombocytopenia to only 9 to 14 days following high dose chemotherapy.

The only randomised study using high-dose chemotherapy as consolidation treatment during first-line therapy for advanced metastatic disease has shown no benefit for the high-dose chemotherapy arm. Patients in this French study were treated with a 4-drug regimen of cisplatin, vinblastine, etoposide and bleomycin (PVEB) either given for 4 cycles, or for 2 cycles followed by high-dose chemotherapy.[85] However, final interpretation of this study remains difficult because of the regimens used (especially the relatively low dose intensity of the 'high-dose' arm) and the imbalance in the number of patients receiving the full treatment on both arms.

The GTCSG uses high-dose chemotherapy (PEI regimen) given as initial treatment. The rationale of an early dose intensification is to achieve a high dose intensity before the development of drug resistance. Between 1990 and 1995, 141 patients with advanced disease criteria (according to the Indiana University classification) were entered on 5 different dose levels (standard and high dose levels 6 to 9).[86] Retrospective assignment of IGCCCG classification revealed 99 patients with poor prognosis and 42 with intermediate prognosis. After a median follow-up of 2.6 years, a 2-year survival rate of 70% and 89% totalling all dose levels was achieved for poor and intermediate prognosis patients, respectively. If these results are confirmed or even improved at the higher dose levels 6 to 8 tested from 1995 to 1998, a 10 to 20% absolute improvement in cure rates might be anticipated with the use of initial consecutive cycles of the high-dose PEI regimen. It remains essential that this investigational treatment is performed in centres with extensive experience, because of its potential toxicity. 11 of 141 patients (8%) died early from tumour- or treatment-related causes.

Despite the convincing hypothetical background and the optimistic results reported, the use of first-line high-dose chemotherapy in testicular cancer patients with a poor prognosis still needs to be performed within clinical trials. In 1996, a US Intergroup study started randomising patients with intermediate and poor prognosis germ cell tumours to either 4 cycles of standard PEB therapy or 2 cycles of PEB followed by 2 cycles of high-dose chemotherapy with cyclophosphamide, etoposide and carboplatin (CEC) with PBSC transplantation. Currently the EORTC is discussing a randomised study in poor prognosis patients, comparing 4 cycles of PEB to sequential high-dose chemotherapy with the PEI regimen. It also appears worthwhile to further optimise the high-dose PEI regimen by reducing treatment toxicity and further increasing efficacy, for example by the addition of paclitaxel. A pilot study of high-dose PEI plus paclitaxel has recently been initiated in Germany (University of Tübingen).

7. Management of Residual Disease After Chemotherapy

Secondary resection of residual tumour masses after chemotherapy is an established part of the comprehensive management of metastatic NSGCT. In general, there is no clear consensus about the size of the residual mass at which a surgical exploration is indicated. About 15 to 20% of residual tumours in patients with normalised tumour markers after chemotherapy will histologically still contain undifferentiated tumour, 45 to 50% necrotic tissue and 30 to 40% differentiated (mature) teratoma.[87] In our series of 109 patients who underwent secondary resection after first-line chemotherapy, undifferentiated tumour and differentiated (mature) teratoma were found in 27 and 21% of patients, respectively.[88] Surgical resection of differentiated teratoma is useful to prevent recurrent teratoma or a subsequent malignant transformation. A relapse rate of 5 to 10% is estimated depending on the completeness of surgical resection.[89-91] For patients harbouring necrotic tissue or undifferentiated tumour in residual masses, it would be useful to iden-

tify these before the operation in order to prevent surgery-related morbidity and mortality. Although the first group of patients needs no further treatment at all, the second group qualifies for salvage chemotherapy.[92]

A model for prediction of the histology of residual masses in NSGCT was presented recently.[93] Independent predictive factors for necrotic tissue were:

- absence of teratomatous elements in the primary tumour
- normal AFP/hCG values before chemotherapy
- elevated LDH
- small pre- and postchemotherapy masses
- shrinkage of the masses by more than 70% during chemotherapy.

Factors distinguishing undifferentiated tumour from differentiated teratoma were:

- higher prechemotherapy LDH level
- larger postchemotherapy mass
- smaller relative shrinkage of the mass.

The proposed model was found to be useful to predict necrotic tissue, but in contrast showed a low ability to distinguish between undifferentiated tumour and differentiated (mature) teratoma.[94] Therefore the best approach is resection of all residual mass if feasible. Some authors recommend a surgical intervention for all patients with initially bulky disease in the retroperitoneum, irrespective of the results of postchemotherapy CT scans.[95]

Survival data for a total of 893 patients with metastatic NSGCT undergoing secondary resection of residual tumour masses after first-line cisplatin-based chemotherapy are summarised in table VII.[88,95-101] These data confirm that 72 to 89% of patients will remain disease-free at 3 years after secondary resection. The finding of necrotic tissue and/or differentiated (mature) teratoma in the resected specimens resulted in 78 to 92% and 67 to 95% long term survival rates, respectively.

Undifferentiated tumour in the resected specimens may indicate a poor prognosis. In 1981, Einhorn et al.[92] reported that patients with undifferentiated tumour at postchemotherapy resection have a long-term survival rate of only 10%. Other investigations have shown that the use of additive cisplatin-based chemotherapy may improve the outcome of patients after the resection of undif-

Table VII. Results of trials of secondary resection after cisplatin-based chemotherapy for metastatic nonseminomatous germ cell tumours (adapted from Hartmann et al.[88])

Reference	n	Disease/progression-free survival (%)				Overall survival (months)				Follow-up (months)	Comments
		nec	td	vt	all	nec	td	vt	all		
Fossa et al.[98]	101	92	95	58	89	92	86	58	94	55 (1-102)	
Mulders et al.[99]	55	-	-	-	72	93	92	27	78	36 (5-96)	Included 15 patients with seminoma + 10 without complete marker normalisation
Hendry et al.[97]	231	-	-	-	-	93	88	41	80	60[a]	
Steyerberg et al.[101]	86	-	-	-	85	-	-	-	87	60[a]	
Toner et al.[95]	157[b]	-	-	-	-	93	88	45	-	60[a]	Included postoperative chemotherapy in case of vt
Fox et al.[96]	43	-	-	56	-	-	-	56	-	36	Follow-up of surviving patients, included postoperative chemotherapy in 27 patients
Gerl et al.[100]	111	77	80	62	77	85	83	77	83	60[a]	Included postoperative chemotherapy in case of vt
Hartmann et al.[88]	109	78	67	66	72	90	83	77	84	60[a]	Included postoperative chemotherapy in case of vt

a Estimated 5-year survival according to Kaplan-Meier calculation.

b Study included 185 patients; survival data are only available for patients who underwent retroperitoneal resection.

n = number of patients; **nec** = necrosis; **td** = differentiated teratoma; **vt** = undifferentiated tumour; **-** = data not available.

ferentiated tumour, with 56 to 70% of patients remaining disease-free at 3 years.[97,101-103] Three investigations demonstrated clear differences for disease-free survival between patients receiving postoperative chemotherapy or no further treatment.[96,102,103] Currently a retrospective international investigation, guided by the Institute Gustave-Roussy in France, is being performed to clarify the outcome of patients with undifferentiated tumour at resection of residual tumours after first-line chemotherapy.[104]

Further problems occur in patients requiring multiple resections. A high incidence of dissimilar histological findings from different localisations is reported within the same individual, ranging from 25 to 47% in 6 studies.[105-110] In our series, 8 of 27 patients (30%) had dissimilar histological findings when comparing retroperitoneal and pulmonary sites.[110] Thus, the recommended approach is to resect all residual tumour masses if technically feasible – either as a single-stage or sequential operation.[106,110]

The complication rate of postchemotherapy RLA is higher than that of primary RLA, but there is no consensus on the type of the abdominal surgical procedure. In selected patients without severe postchemotherapy desmoplastic changes, it is occasionally technically possible to identify sympathetic nerves and manage them by a restricted intervention. Coogan et al.[111] reported that among 472 patients who underwent postchemotherapy RPLND between 1988 and 1995, a select subset of 93 patients (19.7%) underwent nerve-sparing procedures after chemotherapy. 81 of these patients were evaluable for aspects of ejaculatory status and follow-up. Most of them had relatively low volume unilateral adenopathy before induction chemotherapy. After a mean follow-up of 35 months, 76% patients reported normal ejaculation, and 10 pregnancies have been reported. 6 patients relapsed after RLA, but no infield recurrences were observed. On the other hand, a formal RPLND (i.e. RLA) is still often done, and appears to be the standard approach.[105,106,110]

Necrosis identified at thoracotomy should not rule out resection of retroperitoneal masses, because there is a trend that the retroperitoneum often contains unfavourable histological findings.

Recently, positron emission tomography with labelled 2-fluoro-2-deoxyglucose (PET-FDG) was under investigation in patients with metastatic testicular cancer. PET-FDG imaging may be useful for the detection of undifferentiated tumour. However, the distinction between necrotic tissue and differentiated teratoma may still remain difficult, since both tissues have a relatively low metabolic activity.[112] In patients with multiple residual masses, the combination of a negative PET result at all sites and necrotic tissue found at the retroperitoneal resection may identify patients who can be spared from resections at other sites. Another important advance for PET-FDG could be the identification before the operation of patients with undifferentiated tumour, in order to proceed rapidly to salvage chemotherapy.

The management of postchemotherapy residual masses in patients with seminoma is also a controversial issue. Perioperative morbidity has been reported to be higher because of the severe desmoplastic reaction and obliteration of tissue planes.[113,114] Consequently, the low risk of 10 to 15% for undifferentiated tumour in the residual mass, and the absence of differentiated teratoma, might support a policy of observation. The MSKCC reported that a residual mass greater than 3cm predicted a higher likelihood of residual seminoma, but this is now a rare observation. Nevertheless, resection (or multiple biopsies in irresectable disease) of a residual mass >3cm was preferable to follow-up alone.[114,115] The use of additive radiotherapy for residual tumour after completion of chemotherapy for metastatic seminoma has not revealed a substantial benefit.[116]

8. Management of Relapse After Chemotherapy

The second subgroup of patients with NSGCT with an unfavourable prognosis are those who do not respond adequately to primary chemotherapy

or who relapse thereafter.[117] Before the application of salvage chemotherapy, the diagnosis of relapse should be confirmed by additional diagnostic procedures. There are a number of possible situations, as follows.

(i) The appearance of nodular lesions at the end or soon after completion of chemotherapy, despite normalisation of tumour markers, may indicate bleomycin-induced pulmonary injury.

(ii) In the case of progressing metastases despite tumour marker normalisation, growing teratoma syndrome can be anticipated and induction chemotherapy should be completed with subsequent surgical resection.

(iii) Elevated marker concentrations, especially of hCG, without clinically active disease may be due to laboratory error, cross-reactivity with luteinising hormone, marijuana abuse, or the presence of sanctuary sites such as occult central nervous system or testicle metastases; high tumour burden and initial values >50 000 U/L can lead to a 'marker plateau'.

(iv) False-positive elevation of AFP may be due to hepatoma, cirrhosis or hepatitis.

(v) Systemic remission and rising markers may indicate sanctuary sites.

Whereas vinblastine has never been investigated as a single agent, etoposide, ifosfamide and paclitaxel have activity in patients pretreated with, or refractory to, cisplatin. Although patients with relapsed disease will still achieve objective remissions in the range of 30 to 60% with the various conventional regimens of salvage chemotherapy, only 20% are long-term survivors (table VIII).[118-130] Potential prognostic factors for a favourable outcome of standard-dose salvage treatment are achievement of complete remission after induction chemotherapy, testicular primary lesion and limited stage at relapse.[120]

A considerable number of phase II studies investigating high-dose chemotherapy with stem cell transplantation as a treatment option for relapsed testicular cancer have been conducted.[131,132,133-143] Most of these studies have investigated the combination of high-dose carboplatin and etoposide alone, or have added either cyclophosphamide or ifosfamide as a third drug.[131-133,135,137,139-142] It has not yet been clearly demonstrated whether the incorporation of a third drug improves the treatment results.[144] Table IX summarises the results of high-dose chemotherapy regimens in relapsed testicular cancer.[82-84,131-134,137-140,142,143]

Table VIII. Results of standard-dose salvage chemotherapy in relapsed or refractory testicular germ cell cancer

Reference	Regimen	n	CR/PRm– (%)	Relapse from CR/PRm– (%)	Overall relapse-free (%)
Bosl et al.[121]	PEI	45	18	50	9
Hainsworth et al.[122]	PE ± others	45	43	53	20
Pizzocaro et al.[123]	PE ± others	18	44	50	22
Loehrer et al.[124]	PEI or V	48	37	56	15
Motzer et al.[120]	PEI	42	24	40	15
Harstrick et al.[118]	PEI	30	53	88	7
Josefsen et al.[125]	Various	55	78	67	25
Ledermann et al.[126]	Various	38	47	28	39
Gerl et al.[127]	Various	67	57	66	22
Farhat et al.[128]	Various	54	44	58	19
McCaffrey et al.[129]	PEI or V	56	36	35	23
Motzer et al.[119]a	PIT	21	71	13	57 (1-year)
Loehrer et al.[130]	PIV	135	47	49	24

a Good prognosis patients only.

CR/PRm– = complete response or partial response with negative markers; **E** = etoposide; **I** = ifosfamide; **n** = number of patients; **P** = cisplatin; **T** = paclitaxel; **V** = vinblastine.

Table IX. Phase II trials of high-dose chemotherapy in patients with multiply relapsed testicular cancer

Reference	Year	Regimens	n	CR/NED (%)	
				initial	continuous
Wolff et al.[83]	1984	E	11	20	0
Blijham et al.[82]	1981	ECyc	13	40	0
Mulder et al.[84]	1988	ECyc	11	18	9
Pooled data			**35**	**26**	**3**
Nichols et al.[131]	1989	CE	33	25	12
Broun et al.[132]	1992	CE	38	24	13
Rosti et al.[137]	1992	CE	17	33	7
Broun et al.[134]	1995	CE × 2	33	14	7
Lampe et al.[142]	1995	CE × 2	23	37	26
Pooled data			**144**	**27**	**13**
Droz et al.[143]	1993	PECyc	25	38	24
Linkesch et al.[133]	1992	CECyc	41	32	24
Motzer et al.[139]	1996	CECyc	58	40	21
Siegert et al.[140]	1994	CEI	68	31	28
Margolin et al.[138]	1996	CEI × 2	19	40	40
Pooled data			**227**	**36**	**26**

C = carboplatin; **CR/NED** = complete remission/no evidence of disease; **Cyc** = cyclophosphamide; **E** = etoposide; **I** = ifosfamide; **n** = number of patients; **P** = cisplatin.

Based on an analysis of 283 patients who received salvage high-dose chemotherapy at 4 centres, 5 prognostic factors were identified that affected the efficacy of this approach (table X).[144] Three groups of patients were defined by a prognostic score. The 3-year failure-free survival rate for all 283 patients was 29%, but those patients with a score of 0 had a survival rate of 51%, and those with a score of 1 to 2 had a survival rate of 27%. Patients with prognostic score values >2 had a survival rate less than 5% and thus did not benefit from high-dose chemotherapy. These results allow the selection of patients who may benefit most from high-dose chemotherapy and will help to compare the results reported in different studies.

Another important factor is the treatment situation in which salvage high-dose chemotherapy is employed. It may not only be used in patients with second or subsequent relapses, when conventional treatment is no longer considered curative, but also as intensification of first salvage, where conventional chemotherapy may still offer some curative potential.

Summarising the potential impact of high-dose chemotherapy in relapsed testicular cancer, it might be speculated that a 10 to 20% improvement in prognosis – increasing long-term survival rates from 20 to 35% – may be achievable in patients with chemosensitive disease. Currently, there is 1 ongoing study (EBMT-IT94) which randomises patients at first relapse to receive either 4 cycles of standard-dose cisplatin/ifosfamide-based chemotherapy or 3 cycles followed by 1 cycle of high-dosage carboplatin/etoposide/cyclophosphamide (CECyc) plus autologous stem cell transplantation.

8.1 Role of Surgery After Salvage Chemotherapy

The histological findings in resected masses following second-line or salvage chemotherapy differ from those observed following primary chemotherapy, since undifferentiated tumour occurs in approximately 50 to 80% of specimens, 'differentiated teratoma' in 10 to 40%, and necrosis in only 10%. In general, surgery should be avoided in patients in whom serum tumour markers remain elevated after salvage chemotherapy. However, surgery may have some curative potential in a selected group of patients with increased marker levels for

whom no other treatment option exists.[145,146] It appears that patients with a solitary retroperitoneal mass and increased AFP are the best candidates for 'salvage' surgery in an experienced centre. In 1996, we reported 14 of 25 patients with complete resection of residual masses after salvage chemotherapy.[88] In 4 of 5 patients, undifferentiated tumour was found in the resected specimens and application of further chemotherapy did not affect long-term survival.

8.2 Late Relapse

Although the overwhelming majority of relapses will occur within the first 2 years, late relapses after a 24-month disease-free interval have been described in 2 to 4% of patients. Two subgroups of patients have been observed. The first group, formed by patients with isolated mature teratoma, had a good prognosis after excision. The latter cohort includes patients with marker-positive carcinoma who recurred with large volume disease. These patients do not respond very well to chemotherapy, and aggressive surgery is required in almost all patients.[147]

9. New Drugs for the Treatment of Testicular Cancer

Patients relapsing after conventional or high-dose chemotherapy have an extremely poor prognosis.[20,117,144] For these patients, identifying new agents with significant antitumour activity in germ cell cancer remains a priority. A number of drugs, such as vinorelbine, topotecan or retinoids, have failed to demonstrate significant antitumour activity. Etoposide given orally over a prolonged period of time has demonstrated some activity even in patients refractory to standard-dose intravenous etoposide and is employed as palliative treatment.

Table X. Unfavourable prognostic factors for long-term survival after high-dose chemotherapy[144]

Factor	Score value
Primary mediastinal germ cell cancer	1
Disease progression prior to high-dose chemotherapy	1
Refractory disease before high-dose chemotherapy[a]	1
Absolute refractory disease before high-dose chemotherapy[b]	2
hCG >1000 U/L prior to high-dose chemotherapy	2

a At least stable disease or better achieved, but progression within 4 weeks after last cisplatin-based chemotherapy.

b Never achieved stable disease despite cisplatin-based chemotherapy.

hCG = human chorionic gonadotropin.

Since the mechanism of action of paclitaxel differs from those of DNA-damaging agents such as cisplatin and ifosfamide, its role in cisplatin-resistant tumours remains an important clinical issue.[148,149] *In vitro* studies have shown activity in cisplatin-sensitive and -resistant testicular cancer cell lines.[119,150] Table XI summarises the results of phase II trials of single-agent paclitaxel in relapsed testicular cancer.[151-154] There was an overall response rate of 23% in 83 patients, with some patients even achieving a complete remission. Common adverse effects were grade III/IV neutropenia in approximately 40 to 50% of patients, with fever and hospitalisations being reported in 20%, as well as (mostly reversible) neurotoxicity in 12 to 29%. Currently, various combinations of paclitaxel with ifosfamide, with cisplatin and with both agents (TIP regimen) are being investigated.[119,153,155] The TIP combination regimen is used by the GTCSG in patients with first or subsequent relapse of testicular cancer. 3 cycles of the TIP regimen are given to reduce the tumour burden and to allow harvesting of PBSC, followed by consecutive treatment with high-dose chemotherapy with carboplatin, etoposide and thiotepa (TEC).[156,157]

Other new agents are being investigated with paclitaxel as part of first salvage combination chemotherapies in refractory patients. The nucleoside analogue gemcitabine has been found to be active, with 19% partial response or a marker decline >90%, leading to a median progression-free survival of 4 months in 31 evaluable patients.[158] Another ongoing programme at the University of Tübingen is evaluating the role of oxaliplatin in this setting.

Table XI. Activity of paclitaxel in relapsed and/or cisplatin-refractory testicular cancer

Reference	Dose and schedule (mg/m^2)	No. of patients	Response rate (%) [CR/PR]
Bokemeyer et al.[151]	135 to 225; 3- or 6-hour infusion	10	30 [0/3]
Motzer et al.[152]	250;[a] 24-hour infusion	31	26 [3/5]
Bokemeyer et al.[153]	225; 3-hour infusion	24	25 [2/4]
Sandler et al.[154]	170; 24-hour infusion	18	11 [0/2]
Pooled data		**83**	**23 [5/14]**

a With routine use of granulocyte colony-stimulating factor.

CR = complete response; **PR** = partial response.

10. Toxicity of Chemotherapy

The acute adverse effects of chemotherapy are generally controllable. To avoid acute nausea and vomiting after cisplatin-based chemotherapy, the administration of a 5-HT_3 antagonist with dexamethasone appears to be the best approach.[159] Acute nephrotoxicity of cisplatin occurs in nearly all patients[160,161] and makes prophylactic intensive hydration and mannitol/diuretics mandatory. Despite these safety measures a reduction in glomerular filtration rate may follow high cumulative doses of cisplatin. An increase in serum creatinine from pretreatment baseline is a late sign of nephrotoxicity caused by the high functional reserve of the kidney. Ifosfamide may enhance the nephrotoxicity of cisplatin.[120,162] Ongoing trials are investigating the potential of the aminothiol amifostine or the flavonoid silibinin as a nephroprotectant agent.[162-164]

Myelosuppression is frequent following chemotherapy with PEB, but more pronounced following chemotherapy with PEI.[77] Neutropenic fever occurs in 20 to 40% of patients receiving dose-escalated schedules containing ifosfamide. This may define the need for the prophylactic use of CSFs, particularly for patients receiving salvage chemotherapy.[165] The prophylactic use of granulocyte CSFs in patients receiving first-line chemotherapy for advanced disease seems to improve the delivery of the planned treatment and may lead to a reduction in the number of deaths caused by toxicity.[166] Anaemia occurs in most patients, but infrequently results in the need for red blood cell transfusions during first-line chemotherapy. Severe thrombocytopenia is uncommon in first-line cisplatin-based chemotherapy, but occurs more often during salvage chemotherapy.

With the success of modern chemotherapy regimens, the evaluation of long-term toxicity has become an issue of clinical research.[167-169] Patients are usually between 25 to 35 years of age and can expect a normal life-span after successful treatment. A decrease in quality of life, an increased risk for secondary morbidity and the use of economic resources to treat late toxicity may be avoided with the reduction of therapy-induced complications. Numerous publications have demonstrated: oto-, neuro- and nephrotoxicity following the application of cisplatin; neurotoxicity and vascular complications – particularly Raynaud's phenomenon – after vinca alkaloids; vascular toxicity or pulmonary fibrosis after bleomycin; and the substantial impact of many cytotoxic agents on fertility.[167-175]

In a recent investigation of the extent and the reversibility of these late effects after chemotherapy in long-term survivors of testicular cancer, the influence of therapeutic and patient characteristics on the occurrence of late toxicity, as well as the relationship between different types of toxicity, was assessed.[167,172,175] These incidences of transient and persistent long term toxicities after chemotherapy are given in table XII. Alterations of gonadotropin levels (follicle-stimulating hormone, luteinising hormone) occurred in up to 60% and Leydig-cell insufficiency persisted in one-third of the patients. The most frequent symptomatic toxicities were Raynaud's phenomenon in 30%, ototoxicity in 21% and peripheral neuropathy in 17%. In addition, a substantial impact on cardiovascular risk factors was identified in one-fourth of the pa-

tients. 15% of patients exhibited either grossly elevated serum cholesterol levels (with or without obesity) or severe arterial hypertension following chemotherapy. The major risk factor for the development of most toxicities was the cumulative dose of cisplatin applied. A significantly increased frequency of oto-, neuro-, and gonadal toxicity as well as arterial hypertension was observed in patients receiving a cumulative dose of >400 mg/m^2 of cisplatin. Furthermore, subjective impairment caused by late toxicity was also correlated with the cumulative dose of cisplatin applied.[167] Individual patient characteristics, apart from the cumulative dose of the cytostatic agents applied, were of minor importance (smokers, older age) except for ototoxicity (previous noise exposure).[176] Another important finding was the detection of hormonal imbalances, particularly influencing steroid-hormone synthesis and cholesterol levels, in approximately one-third of patients.[175,177]

Fertility aspects are also a major concern. However, the tumour itself reduces fertility before treatment in up to 50% of patients. Additionally chemotherapy may affect the germinal epithelium directly. Compensated hypogonadism, as described above, is frequent.[175,178,179] Recovery appears to peak within 2 years after treatment, more often in younger men. Unfavourable predictive factors for the recovery of spermatogenesis were low prechemotherapy sperm counts, the use of cisplatin and more than 4 cycles of chemotherapy.[178] Sperm banking may be beneficial even for patients who are subfertile at the time of diagnosis, because the techniques of sperm preservation and *in vitro* fertilisation are advancing rapidly. Fertility aspects after treatment may also impact on sexual functioning and quality of life.[180]

Apart from metachronous testicular cancer appearing in the contralateral testis, which occurs in about 2 to 4%, second malignancies are a rare finding. However, an elevated risk for more than 20 years after diagnosis has been reported.[181] Secondary leukaemias characterised by translocations involving chromosome 11q have been reported in fewer than 0.5% of patients receiving a total dose of <2 g/m^2 of etoposide.[182,183] This type of leukaemia may affect up to 2% of patients receiving total etoposide doses >2 g/m^2.[184,185] Secondary leukaemias have to be differentiated from primary mediastinal NSGCT-associated haematological disorders, which represent a biological phenomenon and not a treatment-related effect. These disorders predominantly affect the megakaryocytic lineage, resulting in acute megakaryoblastic leukaemia [AML, French American British Classification (FAB) M7], myelodysplasia with abnormal megakaryocyte or idiopathic/essential thrombocytosis.[186]

The occurrence of secondary solid tumours, for example gastrointestinal malignancies and sarcomas, has been attributed to the use of radiation therapy.[23,187] Overall, a 2- to 3-fold increased risk for secondary malignancies can be found in comparison to the general population.[171] Clearly, the occurrence of these malignancies does not outweigh the enormous benefits of treatment.[188]

Table XII. Long-term toxicity after cisplatin-based chemotherapy in testicular cancer. Results from 90 patients at Hannover University Medical School (adapted from Bokemeyer et al.[167])

Duration	Incidence (%)				
	ototoxicity[a]	neurotoxicity[b]	Raynaud's syndrome[c]	arterial hypertension	gonadal toxicity[d]
Persistent	21	17	30	15	63
Transient	9	33	7	–	ND
Total	30	50	37	15	63

a By audiometric evaluation.

b According to clinical investigation.

c Evaluated by light plethysmography and Doppler-ultrasound investigation.

d According to hormonal evaluation.

ND = not investigated.

11. Conclusion

Testicular germ cell tumours are a highly curable malignancy even in the presence of metastases, with an overall survival rate of approximately 90 to 95% when all stages are considered. The widespread application of high-dose chemotherapy with PBSC, and the use of new cytotoxic agents, makes it mandatory to evaluate the possible late toxicity of these drugs in order to optimize the treatment of testicular cancer patients. Thus, testicular cancer has not only become a model for a curable chemosensitive disease, but also for the study of treatment-associated adverse effects of modern oncological therapies.

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