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Advances in the Treatment of Testicular Cancer

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Abstract

Testicular cancer is the most common solid tumour in young men, and the treatment of testicular germ cell tumours (TGCT) has been called a success story of medical oncology, germ cell cancer being regarded as the "model of a curable neoplasm". Even with metastatic disease, high cure rates can be achieved: the overall 5-year survival for all stages of TGCT is approximately 80%. Today, elaborate systems for prognostic evaluation for gonadal and extragonadal germ cell tumours facilitate the choice of the most appropriate therapy for individual

patients. In doing so, the ultimate goal of treatment is tumour-free survival for any patient with TGCT.

This goal has already been reached for >99% of the patients with early-stage tumours, as well as for the majority of patients with advanced disease (56% of patients with metastases are considered to have a good prognosis at the time of diagnosis; the 5-year survival rate for this group is 90%). However, patients with 'intermediate' or 'poor' prognosis at the time of diagnosis, as well as patients with relapsed disease after cisplatin-containing therapy, still have an unsatisfactorily low 5-year survival rate after standard therapy with PEB (cisplatin, etoposide, bleomycin) of only 80%, 45–55% and 20–25%, respectively.

Therefore, our goals must be (i) to limit acute and chronic toxicity by avoiding overtreatment for patients with localised disease and/or good prognosis with advanced disease; and (ii) to identify patients with poor prognosis and treat them in specialised centres, where not only is optimal interdisciplinary care available but new treatment strategies are being applied. For example, tandem high-dose chemotherapy regimens might be effective in achieving higher cure rates in these patients.

Testicular cancer is the most common solid tumour in young men, and the treatment of testicular germ cell tumours (TGCT) has been called a success story of medical oncology.[1,2] The major reason for the success in the treatment of TGCT is the exquisite sensitivity of germ cell cancer cells to chemotherapeutic agents and radiation. Further understanding of the pathobiology of germ cell tumours, the introduction of new chemotherapeutic substances, and the optimised combination of known cytotoxic agents have resulted in remission rates unparalleled in the field of medical therapy of solid tumours. Furthermore, a large body of evidence from clinical trials has allowed us to implement treatment guidelines that facilitate decision making in the clinic and ensure optimal therapy for all stages of germ cell cancer anywhere in the world.

In spite of these achievements, the practical use of the huge amount of available treatment options still poses a challenge to physicians. Specifically, early-stage patients are at risk of being overtreated, whereas high-risk patients with advanced, refractory or relapsed disease are still difficult to treat. While long-term chemotherapeutic adverse effects may impede the quality of life of the first group, the latter still have a low cure rate and might need intensified treatment.

This article summarises the current guidelines for the treatment of TGCT and provides arguments for our personally favoured treatment options where applicable.

1. Classification Systems for Testicular Germ Cell Tumours (TGCT)

1.1 Lessons from Development

Decisive factors for clinical outcome in patients with TGCT are still clinical characteristics such as mediastinal location of the tumour and, especially, tumour sensitivity to treatment. With a more in-depth understanding of developmental processes as well as genetic and epigenetic characteristics of germ cell tumours, we might be able to draw conclusions for a more efficient treatment.

Germ cell tumours consist of a heterogeneous spectrum of neoplasms and originate in a variety of primary tissues. The anatomical distribution not only to the gonads but also to different extragonadal midline structures most probably results from the route of primordial germ cells (PGCs) during early human development. PGCs are singled out early in development (at week 5–6 in humans) in the extraembryonic mesoderm, and then proliferate and migrate into the genital ridge in the embryo proper, where they differentiate into either pre-spermatogonia or oocytes, depending on the genotype of the somatic neighboring cells in the genital ridge and the resultant microenvironmental characteristics.

During this process, extragonadal PGCs normally undergo apoptosis.[3]

On the basis of patient gender and age at clinical diagnosis, as well as histology and anatomical location of the germ cell tumour, Oosterhuis et al.[4] have proposed a new classification of five GCT entities. Within the testis, they proposed three different entities: (i) the teratomas and yolk sac tumours of newborn and infants (type I tumours); (ii) the seminomas and nonseminomas of adolescents and young adults (type II tumours), referred to as TGCT when located in the testis; and (iii) the spermatocytic seminoma of the elderly (type III tumours). The 2003 WHO classification system for TGCT has adopted this nomenclature.[5]

The scientific significance of this new classification is the notion that each of the three groups of human TGCT might be derived from germ cells with maturational arrests at different stages of development. Therefore, the rapidly evolving field of human developmental biology may contribute to our understanding of the pathobiology of disease. The clinical impact obviously lies in a better understanding of the tumour cell type, especially when it comes to the natural course of disease, as well as response or resistance to therapy. Whereas embryonic characteristics may be associated with either efficient DNA repair or apoptosis and therefore high sensitivity to cytotoxic agents, somatic differentiation might result in the development of treatment resistance.[6,7]

1.2 Clinical Classification Systems

The Tumor size-lymph Nodes Metastases (TNM) classification of the Union Internationale Contre le Cancer (UICC) is used to define the clinical stage of any patient with a gonadal germ cell tumour (table I and table II). Furthermore, the classification of the International Germ Cell Cancer Collaborative Group (IGCCCG) for patients with advanced disease, which incorporates histology and tumour markers in addition to anatomical tumour distribution, is used to subdivide prognostic groups.

The IGCCCG classification distinguishes three prognostic categories.

- Patients with 'good prognosis' have a germ cell tumour with (i) a seminoma histology of any primary site, but without nonpulmonary visceral metastases, regardless of tumour marker levels; or (ii) a nonseminoma with a testicular or retroperitonieal primary tumour, but without nonpulmonary visceral metastases and with 'good markers' (i.e. α-fetoprotein [AFP] <1000 ng/mL and human chorionic gonadotropin [hCG] < 1000 ng/mg [≈5000 iU/L] and lactate dehydrogenase [LDG] <1.5 upper limit of normal [ULN]). This category includes 90% of seminomas and 56% of nonseminomas, and 5-year progression-free survival (PFS) and overall survival (OS) rates are 82% and 89%, respectively and 86% and 92%, respectively.
- Patients who are considered to have an 'intermediate prognosis' have (i) a seminoma with metastases to nonpulmonary visceral organs or (ii) a nonseminoma of the testis or the retroperitoneum, no nonpulmonary visceral metastases, and 'intermediate markers' (AFP <1000–10 000 ng/mL or hCG <1000–10 000 ng/mg [5000–50 000 iU/L] or LDH <1.5–10 × ULN). This category includes 10% of seminomas and 28% of nonseminomas, and 5-year PFS and overall survival rates are 67% and 72%, respectively and 75% and 80%, respectively.
- The 'poor prognosis' group consists only of patients with nonseminomas, which are either primary mediastinal tumours or have spread to nonpulmonary visceral organs from the testis/retroperitoneum or have 'poor markers' (AFP >10 000 ng/mL or hCG >10 000 ng/mg (50 000 iU/L) or LDH >10 × ULN). This category includes 16% of nonseminomas, and 5-year PFS and OS rates are 41% and 48%, respectively.

The choice of treatment in patients with metastatic disease is based on both the TNM classification and the prognostic factor-based IGCCCG classification.

2. Treatment of Patients with TGCT

2.1 Seminoma Clinical Stage (CS) I

Seminoma patients in clinical stage (CS) I have a substantial risk of locoregional lymph node micrometastases and, as a consequence, a 20% risk of disease progression if no adjuvant therapy is administered after orchiectomy. Risk factors for re-

Table I. Tumor size-lymph Nodes Metastases (TNM) classification (used with the permission of the American Joint Committee on Cancer (AJCC), Chicago (IL). The original source for this material is the *AJCC Cancer Staging Manual*, 6th edition, 2002, published by Springer-Verlag, New York, www.springeronline.com)[8]

Classification	Definition
Primary tumor (pT)[a]	
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 in greatest dimension; or multiple lymph nodes, none >2cm but not >5cm in greatest dimension
N2	Metastasis with a lymph node mass, >2cm but not >5cm in greatest dimension; or multiple lymph nodes, any one mass >2cm but not >5cm in greatest dimension
N3	Metastasis with a lymph node mass >5cm in greatest dimension
Pathologic involvement (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass, ≤2cm in greatest dimension and ≤5 nodes positive, none >2cm in greatest dimension
pN2	Metastasis with a lymph node mass, >2cm but not >5cm in greatest dimension; or >5 nodes positive, none >5 cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass >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 tumor markers (S)	
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 × N and hCG (mIU/mL) <5000 and AFP (ng/mL) <1000
S2	LDH 1.5–10 × N or hCG (mIU/mL) 5000–50 000 or AFP (ng/mL) 1000–10 000
S3	LDH >10 × N or hCG (mIU/mL) >50 000 or AFP (ng/mL) 10 000

a The extent of primary tumour is classified after radical orchiectomy.

AFP = α-fetoprotein; **hCG** = human chorionic gonadatropin; **LDH** = lactate dehydrogenase; **N** = upper limit of normal.

lapse include large tumour size (>4cm) and rete testis invasion.[2,9,10] The almost optimal cure rate in these patients is close to 100%, regardless of these facts. It is achieved with one of three treatment options: adjuvant radiation, watchful waiting with treatment only in the case of relapse, or adjuvant chemotherapy with single-agent carboplatin.[2,11-13] Within an observation period of 3 years, carboplatin at area under concentration-time curve (AUC) ×7 is equally effective as radiation.[13] A retrospective analysis on patients that had been treated with either one or two cycles of carboplatin alone suggests that one course of carboplatin is equally effective as two, but also shows a clear dose-dependent response to

Table II. Stage grouping (used with the permission of the American Joint Committee on Cancer (AJCC), Chicago (IL). The original source for this material is the *AJCC Cancer Staging Manual*, 6th edition, 2002, published by Springer-Verlag, New York, www.springeronline.com).[8] See table I for primary tumour, regional lymph node involvement, distant metastesis and serum tumour marker classification.

Stage	Primary tumour	Regional lymph node involvement	Distant metastasis	Serum tumour markers
0	pTis	N0	M0	S0
I	pT1–4	N0	M0	SX
IA	pT1	N0	M0	S0
IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
IS	Any pT/Tx	N0	M0	S1–3
II	Any pT/Tx	N1–3	M0	SX
IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
III	Any pT/Tx	Any N	M1	SX
IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
IIIB	Any pT/Tx	N1-3	M0	S2
	Any pT/Tx	Any N	M1a	S2
IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

carboplatin, with 4.4% relapses in the group treated with 400 mg/m^2 and 2.5% in the group that received AUC×7.[14] Therefore, two courses with a dose of AUC×5–6 might be an effective way to achieve optimal results.

Whereas carboplatin, radiation and watchful waiting are accepted as standard treatment strategies, a risk-adapted approach has been suggested, which provides adjuvant treatment only for patients predicted to have a high risk of relapse.[15,16] Factors associated with a high risk of relapse are vascular invasion and/or pathological tumour stage pT2 or higher.[17] However, this procedure might need more prospective evaluation.[2] Recently, a large retrospective analysis on 704 patients with stage I disease (421 surveillance, 283 adjuvant radiotherapy) over a 21-year period confirmed the safety of surveillance.[18]

2.2 Seminoma CS IIA/B

The internationally accepted standard treatment in CS IIA/B seminoma is radiotherapy. Treatment results in a relapse-free 6-year survival of 95% for stage IIA and 89% for stage IIB, and overall survival is almost 100%.[19-22] In patients refusing radiotherapy or in patients with large retroperitoneal tumour masses, three cycles of standard-dose cisplatin, etoposide and bleomycin (PEB), or four cycles of etoposide are the accepted alternative treatments. A recent retrospective study of 59 patients found a significant relapse rate after radiotherapy, especially with tumours >3cm in size. The authors infer an increasing role of chemotherapy for CS IIB stages.[23] Single-agent carboplatin should not be used in this setting because of a higher risk of relapse and the absence of an advantage over radiation.[24]

2.3 Nonseminoma CS I

The treatment options in patients with stage I nonseminoma consist of adjuvant chemotherapy, nerve-sparing retroperitoneal lymph node dissection (NS-RPLND) and surveillance. Similar to stage I seminomas, the cure rate of patients with nonseminoma CS I is 99%, independent of the treatment strategy used.[25,26] However, the relapse rate without adjuvant treatment is higher in patients with nonseminoma compared with seminoma (30% vs 20%).[25]

Because vascular invasion has been identified and accepted as a valid prognostic indicator, with a risk of relapse of almost 50% with vascular invasion and 14–22% without vascular invasion,[16,26-28] the choice of treatment is mainly based on the presence or absence of this histological finding. Low-risk patients are usually surveyed and treated only in the case of relapse, thereby still reaching a cure rate of almost 100%.[27,28] Patients without vascular invasion and with the histological finding of mature teratoma had an exceptionally low risk of relapse in a retrospective study of 88 cases.[29]

High-risk patients (with vascular invasion) are usually treated with two cycles of PEB (overall cure rate >99%[26]), although this is an unnecessary and potentially hazardous strategy for 50% of these patients.[30-33] The substitution of vincristine for etopo-

side (BOP) has no advantages over PEB except for a lower incidence of alopecia, but is associated with a higher incidence of neuropathy.[34] Ongoing international studies will clarify whether one course versus two courses of PEB is sufficient for the treatment of high-risk patients.

The surgical option consists of NS-RPLND and has been suggested as an alternative for patients reluctant to receive chemotherapy or undergo regular surveillance, the latter being psychologically stressful to the patient given the high relapse rate of almost 50%.[35-38] The main adverse effect of NS-RPLND is retrograde ejaculation in as many as 6–8% of patients.[25,39,40] Furthermore, the relapse rate after NS-RPLND is 10%, with relapses most often occurring in the lungs.[41]

2.4 Nonseminoma CS IIA/B

Given the overall cure rate for CS IIA and IIB nonseminoma (98%) and the relatively low relapse rate in patients undergoing surveillance after orchiectomy, the decision for or against adjuvant treatment is difficult, especially when patients are clinically suspected to have CS IIA because of small retroperitoneal lymph nodes (1–2cm) and without elevated markers. Thus, watchful waiting with regular surveillance of the retroperitoneal lesions is a reasonable strategy in these patients because a staging NS-RPLND results in overall morbidity in about 10% of patients, loss of antegrade ejaculation being the most common adverse effect.[40,42] A prospective trial has shown that 12–13% of patients suspected of having CS II tumours are found to have pathological stage (PS) I by surgical exploration,[42] but even for PS IIA/B, surveillance is an alternative option to adjuvant chemotherapy.[43-46] Whereas chemotherapy is associated with a recurrence rate between 0% and 7%, with relapses usually occurring outside the retroperitoneum, it represents an unnecessary and potentially hazardous measure in at least 50% of patients.[47-52] In the case of regular surveillance, if progressive disease occurs without a corresponding increase of the tumour markers AFP or β-hCG, explorative surgery is recommended.[2]

The IGCCCG has suggested that patients with stage IIA/B and marker-negative disease be offered an ultrasonography guided biopsy and that those patients with a positive biopsy for undifferentiated tumour receive three cycles of BEP as the treatment of choice. However, patients with abnormal levels of AFP, β-hCG and/or LDH in CS IIA/B are to be treated with PEB, according to IGCCCG recommendations for patients with advanced disease.[2]

2.5 Advanced Disease

Before discussing treatment strategies for each of the three IGCCCG categories, 'good', 'intermediate' and 'poor' prognosis, the special status of seminomas compared with nonseminomas is assessed, with an emphasis on published data regarding the use of cisplatin versus carboplatin in advanced seminoma.

2.5.1 Seminoma IIC/D, III

Primary chemotherapy is the treatment of choice in this group of patients because there is a high relapse rate of 20–30% with radiation alone.[53,54] Seminoma patients are on average about 10 years older than patients with nonseminomatous germ cell tumours, and seminomas are more sensitive to chemotherapy than nonseminomas. Therefore, toxicity is an important issue in this group of patients and the use of carboplatin as a substitute for cisplatin has been extensively studied. Earlier studies showed remission rates of 80–90% with cisplatin-containing standard-dose regimens, as opposed to 77–93% when cisplatin was replaced with carboplatin. Even with single-agent carboplatin treatment, disease-free survival rates of about 75% were reached (table III).[55-66]

In addition, there are three randomised trials comparing cisplatin and carboplatin. The first is a set of 69 patients with 'good risk' disease, according to the Memorial Sloan Kettering Cancer Center (MSKCC) classification,[72] who were treated with four cycles of either cisplatin plus etoposide (PE) or carboplatin plus etoposide (CE). Remission rates were 87% for PE and 94% for CE, and event-free survival rates were 87% for PE and 82% for CE, the latter difference not being significant.[69] In the second trial, four cycles of carboplatin alone (400 mg/m^2) were compared with four cycles of PE in patients with advanced metastasising seminomas. After 130 patients had been recruited, the study had to be stopped because of simultaneously published negative results on the use of carboplatin in non-

Table III. Carboplatin- and cisplatin-containing chemotherapy in advanced seminomas

Study (year)	Regimen	No. of patients	Continual CR rate (%)
Non-comparative trials			
Horwich et al.[58] (1992)	C	70	77
Schmoll et al.[65] (1993)	C	42	71
Mencel et al.[63] (1994)	CE	35	83
Sleijfer et al.[66] (1996)	CIVcr	27	93
Jones et al.[60] (1997)	CCyc	31	77
Pizzocaro et al.[64] (1986)	PVB/PEB	31	75
Logothetis et al.[62] (1987)	P/Cyc	42	92
Fossa et al.[55] (1987)	PVB/PEB	54	78
Loehrer et al.[61] (1987)	PVB/PEB	60	66
Mencel et al.[63] (1994)	VAB-6/EP	105	87
Fossa et al.[56] (1995)	PIVcr	42	90
Horwich et al.[67] (1997)	PEB/PVB	45	93
Bokemeyer et al.[68] (2001)	P-based	103	90
Gholam et al.[57] (2003)	PE(B), VAB-6, PIVcr	145	81
Randomised comparisons			
Bajorin et al.[69] (1993)	PE vs CE	69	87 vs 82 (ns)
Horwich et al.[70] (2000)	PE vs C	130	91 vs 77 (ns)
Clemm et al.[71] (2000)	PEI vs C	280	86 vs 88 ($p < 0.05$)

B = bleomycin; **C** = carboplatin; **CR** = complete response; **Cyc** = cyclophosphamide; **E** = etoposide; **I** = ifosfamide; **ns** = not significant; **P** = cisplatin; **V** = vinblastine; **VAB-6** = cisplatin + vinblastine + dactinomycin + bleomycin + cyclophosphamide; **Vcr** = vincristine.

seminomatous germ cell tumours. Whereas the progression-free 2-year survival was in favour of PE (82% compared with 76%), there was no difference in overall survival.[70,73]

A randomised German multicentre study included 280 patients with advanced seminomas, who were treated with either four cycles of carboplatin or four cycles of cisplatin, etoposide and ifosfamide (PEI or VIP regimen). Whereas the relapse rate was 5% in the PEI group, it was 26% in the carboplatin group ($p < 0.01$). The overall survival rate was 95% in the PEI group versus 87% in the carboplatin group (not significant).[71] A pooled analysis of two randomised trials found single-agent carboplatin to be inferior to cisplatin-based combination therapy; it concludes that single-agent carboplatin should not be recommended as standard treatment for any patient subgroup with advanced metastatic seminoma and that cisplatin-based combination regimens remain the standard of care.[74] Therefore, the international standard therapy for patients with advanced seminomas consists of three or four cycles of PEB in patients with 'intermediate' or 'poor' prognosis (IGCCCG criteria) advanced seminomas, respectively. Carboplatin is only used in individual patients when cisplatin is contraindicated.

2.5.2 'Good Prognosis'

The main objective in 'good prognosis' patients has changed in recent years, and it has become of major importance to reduce treatment-related morbidity without compromising the excellent long-term survival rate.[75,76] Therefore, standard therapy was scaled down from four cycles of cisplatin, vinblastine and bleomycin (PVB×4) in the mid-1980s to three cycles of either a 5-day regimen of PEB or a 3-day regimen of $PE_{500}B$ (etoposide 500 mg/m^2).[69,75-82] Sixty percent of all patients with advanced germ cell tumours belong to the 'good prognosis' subgroup and have a 5-year survival rate of 90%. Attempts to remove bleomycin from the above-mentioned triple combinations to reduce short- and long-term toxicity have been unsuccessful.[78,79] Also, the substitution of cisplatin with carboplatin resulted in a lower relapse-free survival and overall survival (table IV).[67,83]

Today, three cycles of PEB are considered standard therapy. Patients with pre-existing chronic lung disease (diffusing capacity of the lung for carbon monoxide [DLCO] <60%) can alternatively be treated with four cycles of PE.[84] A recent update confirms the high effectiveness of four cycles of PE compared with three cycles of PEB for 'good prognosis' patients.[86] Risk factors for the development of bleomycin-associated pulmonary toxicity are impaired renal function, age >40 years, advanced tumour stage and a cumulative dose of >300mg bleomycin.[87] However, the aforementioned comparative study of four cycles of PE versus three cycles of PEB documented double the number of serious adverse events, including treatment-related deaths in the four-cycle group.[84] Although the difference did not reach significance levels, these results should be kept in mind when treating 'good risk' patients.

Table IV. Randomised trials on metastasised 'good prognosis' testicular germ cell tumours

Study (year)	Classification	Regimens	Aim of trial	CR rate (%)	Continual CR rate (%)	Comment
Bosl et al.[77] (1988)	MSKCC	VAB-6 × 3 EP × 4	New two-drug regimen	96 93	85 82	Equal effectiveness
Bajorin et al.[69] (1993)	MSKCC	EC × 4 EP × 4	Carboplatin vs cisplatin	80 88	87 76	EC × 4 inferior
Loehrer et al.[78] (1995)	Indiana	PEB × 3 PE × 3	No bleomycin	94 88	86 69	PE × 3 inferior
Bokemeyer et al.[83] (1996)	Indiana	CEB × 4 PEB × 3	Carboplatin vs cisplatin	96 97	68 86	CEB × 4 inferior
Horwich et al.[67] (1997)	IGCCCG	CEB × 4 PEB × 4	Carboplatin vs cisplatin	87 94	90 97	CEB × 4 inferior
de Wit et al.[79] (1997)	EORTC	BEP × 4 EP × 4	No bleomycin	95 87	91 83	EP × 4 inferior
Saxman et al.[80] (1998)	Indiana	PEB × 4 PEB × 3	Reduction of therapy	97 98	88 87	Equal effectiveness
Culine et al.[84] (2003)	IGCCCG	PEB × 3 PE × 4	No bleomycin, increase of therapy	92 91	96 92	Equal effectiveness
de Wit et al.[81] (2001)	IGCCCG	PEB × 3 PEB × 3/PE × 1	Reduction of therapy, 5-day vs	Not stated	90 89	Equal effectiveness
		PEB (d_{1-5}) PEB (d_{1-3})	3-day regimen		89 90	Equal effectiveness
Toner et al.[85] (2001)	MSKCC	$PE_{500}B_{90}$ × 3 $PE_{360}B_{30}$ × 4	Indiana vs MRC	90 91	99 88	Indiana superior

B = bleomycin; **C** = carboplatin; **CR** = complete response; **E** = etoposide; **EORTC** = European Organisation for Research and Treatment of Cancer; **IGCCCG** = International Germ Cell Cancer Collaborative Group; **MSKCC** = Memorial Sloan Kettering Cancer Center; **P** = cisplatin; **VAB-6** = cisplatin + vinblastine + dactinomycin + bleomycin + cyclophosphamide; × **3, 4** indicates number of cycles.

The dosage of etoposide and/or bleomycin in the PEB protocol varies in different countries. A randomised study comparing the Indiana-PEB (etoposide 100 mg/m^2 on days 1–5, bleomycin 30U on days 1, 8 and 15) to the Medical Research Council (MRC)-PEB (etoposide 120 mg/m^2 on days 1–3, bleomycin 30U on day 1) found a similar response rate of 88% and 87%, respectively.[85] However, overall survival was significantly better with the Indiana-PEB, this difference being the result of a higher number of tumour-associated deaths in the MRC-PEB treated group. On the other hand, although dose intensity of the PEB regimen plays an important role for 'good prognosis' patients, PEB can be given over a course of 3 days, as long as a cumulative dose of 500 mg/m^2 of etoposide per cycle is administered.

2.5.3 'Intermediate Prognosis'

The optimal treatment for patients with intermediate prognosis has not been fully established, because this subgroup has only been defined since 1995 as a result of an IGCCCG meta-analysis. Therefore, there are no data from completed prospective studies. A randomised clinical trial comparing ifosfamide instead of bleomycin combined with cisplatin and etoposide (PEI×4 vs PEB×4) in a similarly defined subgroup of patients showed long-term survival rates of 83% for the PEB-treated and 85% for the PEI-treated patients, albeit at the cost of increased toxicity in the PEI group.[88] The trial was discontinued because bleomycin was shown not to be superior to ifosfamide in the 'poor prognosis' group.[89]

Promising treatment strategies for a prognostic improvement are primary high-dose chemotherapy, which is being evaluated for 'poor prognosis' patients, and the addition of new chemotherapeutic drugs to the current standard regimen. At present the European Organisation for Research and Treatment of Cancer (EORTC) is conducting a prospective phase III clinical trial comparing PEB with paclitaxel-PEB. Recent phase II data from studies using alternating chemotherapy regimens such as BOP-CISCA-POMB-ACE (where CISCA is cisplatin, doxorubicin and cyclophosphamide; POMB is cisplatin, vincristine, methotrexate and bleomycin; and

Table V. Randomised trials on metastasised 'poor prognosis' testicular germ cell tumours

Study (year)	Classification	Regimen	Aim of trial	CR rate (%)	Comment
Williams et al.[76] (1987)	Indiana	PVB × 4 PEB × 4	Etoposide instead of vinblastine	38 63	PVB inferior
Wozniak et al.[101] (1991)	SWOG	PVB × 4 PEV × 4	Etoposide instead of bleomycin	77 73	Equal effectiveness
Ozols et al.[100] (1988)	NCI	PVB × 4 $P_{(200)}$EBV × 4	Addition of etoposide and doubled cisplatin dose	67 88	PVB inferior
Nichols et al.[103] (1991)	Indiana	PEB × 4 $P_{(200)}$EB × 4	Doubled cisplatin dose	73 68	No benefit of dose increase
de Wit et al.[97] (1995)	EORTC	PEB × 4 PVB/BEP × 2	Alternating regimens	72 76	Equal effectiveness
Nichols et al.[89] (1998)	Indiana	PEB × 4 PEI × 4	Ifosfamide instead of bleomycin	60 63	Equal effectiveness, increased toxicity with ifosfamide
Kaye et al.[99] (1998)	MRC/EORTC	PEB × 6 BOP/VIP-B × 3	Sequentially alternating regimens	57 54	Equal effectiveness
Droz et al.[98] (2001)	IGCCCG	PEB × 4 CISCA/VB × 4–6	Sequentially alternating regimens	57 54	Equal effectiveness

B = bleomycin; **CISCA/VB** = cisplatin + doxorubicin + cyclophosphamide; **CR** = complete response; **E** = etoposide; **EORTC** = European Organisation for Research and Treatment of Cancer; **I** = ifosfamide; **IGCCCG** = International Germ Cell Cancer Collaborative Group; **MRC** = Medical Research Council; **NCI** = National Cancer Institute; **O** = vincristine; **P** = cisplatin; **SWOG** = Southwest Oncology Group; **V** = vinblastine; **VIP-B** = etoposide + ifosfamide + cisplatin + bleomycin.

ACE is etoposide, dactinomycin and cyclophosphamide) or reduced dosage CISCA/VB (vinblastine and bleomycin) show disease-free long-term survival rates of 83% (CI 95% 68, 100) and 88% (CI 95% 76, 100) respectively.[90,91]

The present consensus recommendation includes four cycles of standard-dose PEB.[88,92] Importantly, a recent EORTC trial on quality of life found increased gastrointestinal toxicity and an increased risk of tinnitus with four cycles of 3-day PEB compared with four cycles of 5-day PEB.[93] Therefore, if four cycles are planned, the 5-day PEB regimen is recommended. Because of the comparably unfavourable prognosis of this patient group (5-year survival rate 79% [CI 95% 75, 83]), patients should generally be included in prospective studies.

2.5.4 'Poor Prognosis'

According to the IGCCCG, only patients with nonseminomatous germ cell tumours can be classified as 'poor prognosis'. This group of patients shows insufficient cure rates with cisplatin-based combination chemotherapy: four cycles of standard-dose PEB chemotherapy result in a 5-year overall survival rate of 48% (CI 95% 42, 54), with a tendency towards better data in more recent publications on phase III trials.[75,92,94,95]

Compared with standard therapy, the previously tested treatment strategies (e.g. alternating protocols with BOP/VIP-B, CISCA/VB, CBOP/PEB or PVB/PEB [where CBOP is carboplatin, bleomycin, vincristine and cisplatin]) did not result in a significant improvement of either remission or survival rates.[96-99] In addition, the level of toxicity of the alternating protocols was, for the most part, clearly higher.

The results of randomised trials in 'poor prognosis' patients are summarised in table V.[76,100-102] Recently, dose-intensified chemotherapy protocols, including autologous peripheral blood stem cell support, have been dominating the field of experimental therapy of poor prognosis patients. Previous attempts with increased doses of cisplatin in the framework of an otherwise conventionally dosed chemotherapy were both ineffective and highly toxic.[100]

In Germany, a concept of early-dose intensification with sequential high-dose treatments has been investigated. The PEI regimen was used. Tumour cells in large masses are confronted with different invasion pharmacokinetics and cytostatic concentrations, depending on the local perfusion characteristics. Therefore, dose intensification might help to avoid early resistance formation compared with the

typical procedure of high-dose concepts for relapsed or refractory disease. The protocol includes a first cycle of standard-dose PEI-regimen for granulocyte-specific colony stimulating factor (G-CSF) supported blood stem cell mobilisation, as well as three (to four) cycles of high-dose PEI with autologous blood stem cell support.

From 1993 to 1999, 221 patients with 'advanced disease' criteria (Indiana University classification) have been treated with eight different dose intensity levels. The analysis of 182 patients fulfilling 'poor prognosis' criteria in dose levels 3–8 (including peripheral blood stem cell transplantation) showed a 5-year survival rate of 73% after a median observation period of 47 months.[102] However, to date there are no data from an adequate, prospective study that would definitely prove the superiority of high-dose over standard-dose chemotherapy. One retrospective matched-pair analysis comparing patients who had been treated with either high-dose PEI or standard-dose PEB showed increased relapse-free 3-year survival (82% vs 71%) and overall 3-year survival (75% vs 59%) with the high-dose protocol.[104]

Currently, prospective, randomised trials evaluating high-dose chemotherapy in 'intermediate' and 'poor' prognosis patients are being carried out in the US and Europe. The US-Intergroup Study has stopped recruitment of 240 patients and first results will be available in 2006. The EORTC trial has currently recruited >100 of 220 patients. In parallel, trials are being carried out adding paclitaxel to primary high-dose chemotherapy protocols[105,106] However, this procedure did not seem to result in significantly improved treatment results. Recently, a retrospective analysis raised the question of whether tandem high-dose chemotherapy is in fact superior to single high-dose chemotherapy, but prospective studies have not been carried out as yet.[107] Another ongoing European-American phase III trial started in November 2003 and compares BEP×4 to a dose-dense regimen including oxaliplatin, paclitaxel, ifosfamide, bleomycin, etoposide and cisplatin.[108]

Outside clinical trials, standard therapy for 'poor prognosis' patients consists of four cycles of PEB.[102,109] Although four cycles of PEI are no more effective (but more myelotoxic[94]) than PEB, the avoidance of bleomycin-induced lung toxicity is beneficial for patients who need surgical removal of residual tumour masses after induction chemotherapy. It must also be noted, however, that this trial[94] was conducted before the era of haematopoietic growth factors. Alternatively, in patients receiving four cycles of PEB chemotherapy and for whom surgery after chemotherapy is anticipated, it is frequently recommended that the last two doses of bleomycin be deleted (week 11 and 12). Again, although there are no randomised trials supporting this minor deviation, it seems prudent in light of the extensive surgeries these patients face.

In high turnover centres, patients with a particularly large tumour burden are routinely treated with a cycle of reduced-dosage PEB because they tend to have more complications with standard-dose induction. There are no general recommendations for treatment modifications in patients in poor general condition (Karnofsky Performance Status of <50%) or with extensive infiltration of the liver or the lungs.

2.6 Patients with Brain Metastases

Approximately 10% of the 'poor prognosis' patients (i.e. approximately 1–2% of patients with testicular cancer) have brain metastases at initial diagnosis; however, even these patients can expect a long-term survival rate of 30–40% with cisplatin-based chemotherapy alone, cerebral radiotherapy having limited impact on the course of disease.[110] At present, there are no prospective results on the optimum sequence of chemotherapy, radiation and surgery, but chemotherapy is usually the first step of treatment in symptom-free patients, followed by radiation. If the patient reaches a complete remission after chemotherapy alone, consolidating radiation after chemotherapy might not be necessary. Patients with neurological symptoms from their cerebral metastases should be treated with simultaneous chemotherapy and radiation. Primary neurosurgical intervention is limited to patients who cannot be treated with chemotherapy because of the cerebral metastases.

A retrospective multicentre evaluation from the German Testicular Cancer Study Group indicated a significantly improved 5-year survival when whole-brain irradiation was added to chemotherapy.[111] Whether secondary resection of a solitary residual mass is required after chemotherapy (magnetic

resonance imaging [MRI] scans are mandatory for detection of micrometastases) remains to be determined and depends on the extent of systemic disease. Surgery is indicated only in individual patients with resectable solitary brain metastases when other residual lesions are resectable and the initial histology of the primary tumour contained teratoma or the brain tumour displays cystic changes. Primary surgical approaches should be limited to patients who cannot receive induction chemotherapy because of neurological symptoms, in order to prepare them for timely systemic treatment.

2.7 Patients with Hepatic Metastases

There is limited evidence as to the optimal treatment of patients with liver metastases, and the available data are from retrospective studies.[112-115] From these, we can conclude the following: (i) residual hepatic metastases post-chemotherapy contain a large portion of teratoma and vital tumour; (ii) in comparison with other localisation, e.g. the retroperitoneum, hepatic lesions have a large spectrum of different histologies, mainly reflecting an unfavourable prognosis; (iii) the long-term survival rate after surgical removal of residual hepatic lesions (65–75%) is higher than without surgery; and (iv) surgery-related mortality is low in experienced centres actively participating in germ cell tumour protocols (<3%). However, patients with hepatic metastases are often in a poor general condition, which might contribute to a selection bias in the retrospective evidence. Nevertheless, residual hepatic metastases should be removed in eligible patients.

2.8 Special Characteristics of the Treatment of Patients with Germ Cell Tumours of Extragonadal Origin

Approximately 1–4% of all germ cell tumours are primary extragonadal germ cell tumours and are found in midline structures. In retrospective studies, the majority of patients were found to have viable or burned-out testicular cancer. Therefore, the existence of a primary extragonadal origin of these tumours has been questioned.[116] On the other hand, these tumours occur in atypical locations such as the pineal gland or the sacrococcygeal region. Furthermore, there is an association with Klinefelter's syndrome, Down's syndrome and certain haematological neoplasias, which are not treatment related.[117,118]

Because of the small number of patients with extragonadal germ cell tumours, treatment has been performed analogous to TGCT. Mediastinal seminoma patients have a 5-year survival probability of >80%, similar to those with metastasised testicular or retroperitoneal seminomas. Nonseminomatous mediastinal tumours have a poor prognosis, with almost no chance of survival in the case of relapse.[68]

A separate set of prognostic factors has been found for extragonadal germ cell tumours in an international study.[119] Table VI summarises the variables that were found to be of multivariate significance, and table VII displays the resulting score and the corresponding survival rates for each group. Combined with the data gathered from patients with seminomatous germ cell tumours, four subgroups of patients can be defined: 'excellent', 'intermediate low', 'intermediate high' and 'poor'.

A prospective trial evaluating a high-dose chemotherapy concept in 28 patients with primary mediastinal germ cell tumours showed an improvement of the 5-year survival rate by 10–15% in comparison with an international database of 253 corresponding cases treated with conventional cisplatin-based chemotherapy.[120]

2.9 Relapsed Disease

The prognosis of patients not responding to or relapsing after cisplatin-containing therapy is determined by factors such as response to first-line treat-

Table VI. Variables with multivariate significance for the overall survival in patients with extragonadal nonseminomas

Factors for overall survival	P-value	HR	95% CI	Score
Presence of liver metastases	0.006	1.72	1.17, 2.52	1
Presence of lung metastases	0.028	1.43	1.04, 1.97	1
Presence of CNS metastases	0.002	2.53	1.42, 4.52	2
Elevation of β-hCG	0.022	1.48	1.06, 2.08	1
Mediastinal primary tumour	0.000	2.29	1.64, 3.20	2

β-hCG = β-human chorionic gonadotropin; **HR** = hazard ratio.

Table VII. Resulting prognostic categories in patients with extragonadal nonseminomas (for definition of scores, see table VI)

Risk category	No. of pts	CR/PRm− no. (%)	Relapse rate, no. (%)	Survival 1y, 5y (%)
'Excellent' (all seminoma pts)	95	83 (91)	12 (13)	95, 89
'Intermediate low' (score 0 or 1)	109	83 (85)	47 (43)	90, 69
'Intermediate high' (score 2 or 3)	284	185 (71)	136 (48)	80, 55
'Poor' (score >3)	59	22 (39)	46 (78)	49, 17

CR = complete response; **pts** = patients; **PRm−** = partial response and tumour marker normalisation.

ment, localisation of the primary tumour, level of tumour markers and duration of first remission.[121,122]

Both nonseminoma patients with limited disease and seminoma patients with limited disease who relapse after first-line radiotherapy receive cisplatin-based chemotherapy according to the treatment recommendations of advanced disease, thereby reaching a cure rate of >90%.

For patients with relapsed seminoma or nonseminoma after first-line therapy with PEB, long-term remission rates of almost 50% can be reached using conventionally dosed cisplatin-based salvage chemotherapy, although long-term survival can only be achieved for about 20% of patients.[123] Typical examples are PEI (or VIP); vinblastine, ifosfamide, cisplatin (VeIP); or paclitaxel, ifosfamide, cisplatin (TIP);[124] the superiority of one regimen over the other has not been demonstrated for either seminoma or nonseminoma patients.[125,126] Taking into account the aforementioned prognostic criteria, patients with good prognosis can be treated with conventional salvage regimens to avoid treatment toxicity related to high-dose regimens, whereas patients fulfilling poor prognosis criteria should be included in prospective trials aiming to improve dose-intensive treatment concepts.[127,128]

2.9.1 High-Dose Salvage Chemotherapy

High-dose chemotherapy with autologous blood stem cell support has been evaluated in both nonresponding and relapsed disease for almost 20 years. Initial trials using single-agent etoposide or cyclophosphamide, or a combination of both resulted in disappointing long-term survival rates. In 1989, high-dose CE was shown to induce objective remissions in 44% and long-term (>12 months) remissions in 12% of 32 patients at Indiana University.[86] Subsequent trials in the US and Europe confirmed these results with a few modifications in CE regimens. With increasing experience in the management of patients undergoing high-dose chemotherapy and autologous transplantation, this treatment option has increasingly been offered not only to previously incurable patients, but also as second-line therapy at first relapse.

The data regarding early dose intensification in salvage treatment remain controversial. Whereas phase II results are promising,[129,130] no advantage was seen in the only published, large, randomised phase III trial.[131] In an international effort, 280 patients with relapsed disease after primary cisplatin-containing chemotherapy were randomly assigned to receive either four cycles of PEI (or PVI [substituting vinblastine for etoposide]), or three such cycles followed by high-dose carboplatin, etoposide and cyclophosphamide with haematopoietic stem cell support. Complete and partial response rates were 56% in both study arms. More importantly, 3-year event-free survival was only insignificantly increased from 35% to 42% ($p = 0.16$) in the high-dose arm. However, complete responders benefited from the single cycle of consolidating high-dose chemotherapy, their disease-free survival improving from 55% to 75% at 3 years ($p < 0.04$). Therefore, this trial both answers and raises questions. Although a single consolidating cycle of high-dose chemotherapy does not significantly increase overall event-free survival, a subset of patients benefited. In conclusion, the additional beneficial effect of high-dose chemotherapy seems to be <20%, which was the anticipated statistical hypothesis in this trial. This estimation is consistent with retrospective matched-pair analyses.[132] The next step might be to identify patients who will benefit from a high-dose approach. It is mandatory to treat relapsed patients within prospective studies in order to assess the toxicity related to high-dose chemotherapy and to address the principles of early-dose intensification versus late consolidation by high-dose chemotherapy in controlled clinical trials. In Germany, a randomised trial has finished recruitment in this setting.

2.9.2 Secondary Post-Chemotherapeutic Surgery and Salvage Surgery

Residual lesions after primary chemotherapy might represent viable residual disease and are to be removed in order to prevent tumour progression from these manifestations.[133] Patients belonging to a good prognosis IGCCCG group after complete resection of all residual lesions and with <10% viable cells in the histopathological specimens might not even need postsurgical chemotherapy.[134] In addition, recent evidence shows that although discordant histological findings between residual retroperitoneal and thoracic lesions are common, contralateral lung surgery can be avoided when only necrosis is found in the first lung after primary chemotherapy.[135]

Long-term survival of patients with relapsed disease can be achieved in about 25% of patients when the IGCCCG recommendations for salvage surgery are applied.[122,136] Salvage surgery should not be attempted in patients with rapidly progressive disease with increased β-hCG levels.[2]

3. New Drugs in the Treatment of TGCT

Patients with relapsed disease after conventional-dose or high-dose salvage chemotherapy are incurable.[121,137,138] Therefore, the development of new drugs is vital, especially as only a limited number of the currently available new drugs are active in germ cell tumours.

Oral metronomic dose etoposide could induce durable tumor control in individual cases that had not responded to conventional-dose intravenous etoposide.[139]

Paclitaxel shows partial activity in tumours that are nonresponsive to cisplatin.[140-142] Clinical phase II trials confirmed its effectiveness as a single agent[143-145] and, currently, paclitaxel is being evaluated in different combination regimens,[141,143] including high-dose chemotherapy protocols for relapsed disease.[124]

Single-agent gemcitabine induced partial remissions in intensively treated patients and resulted in a median progression-free survival of 4 months.[146,147]

Because cross-resistance against oxaliplatin and cisplatin is incomplete in germ cell tumour cell lines, oxaliplatin has been studied in a trial by the German Testicular Cancer Study Group. Thirty-two patients, of whom 78% had received carboplatin/etoposide-based, high-dose chemotherapy, were treated. A partial remission was achieved in four patients who had cisplatin-refractory disease.[148] In a subsequent trial, 35 patients with intensive pretreatment or nonresponding germ cell tumour were prospectively treated with a combination of oxaliplatin and gemcitabine. The response rate was 46% for the whole group and 44% for the cisplatin-refractory patients.[149] Oxaliplatin has also been shown to induce partial remissions in combination with paclitaxel in these patients.[150]

Paclitaxel and gemcitabine have also been found to induce remissions in patients with nonresponding germ cell tumours. In 28 treated patients, remission rate was 21% and in 2 patients, a disease-free survival of >25 months was achieved.[151]

4. Chemotherapy-Related Toxicity

Although acute adverse effects of chemotherapy are avoidable with supportive therapy,[152,153] long-term toxicity related to chemotherapy remains a problem.

Acute toxicity in the form of myelosuppression occurs after chemotherapy with PEB and PEI,[14] and G-CSF is used prophylactically in intensely treated patients (especially in the case of salvage chemotherapy) to prevent neutropenic fever, which complicates treatment in 20–40% of patients treated with dose-intensified regimens.[154,155] Treatment-related anaemia or thrombocytopenia after three to four cycles of PEB infrequently requires transfusion.

During treatment with cisplatin-containing regimens, germ cell tumour patients carry a higher risk of thromboembolic events compared with patients with other malignant diseases. Elevated serum LDH and a large body surface area (>1.9m^2) were found to be independent risk factors for thromboembolic events in a recent study.[156] The significance of routine thromboembolic prophylaxis in patients at risk is to be determined in a prospective trial.

With the advent of more successful treatment, clinical research has recently focused attention on long-term toxicity.[157-159] Most patients are 25–35 years old and supposedly have an almost normal life

expectancy after successful therapy. A large body of evidence on long-term toxicity is available: ototoxicity, neurotoxicity and nephrotoxicity are dose-limiting in cisplatin treatment. Vinca alkaloids are neurotoxic and vasculotoxic. Bleomycin is known for causing pulmonary fibrosis. In addition, impaired fertility and the risk of secondary malignancy have been areas of concern.[48,160-162] Symptomatic toxicity 5 years after therapy include Raynaud's phenomenon in 30%, hearing impairment in 21% and dysaesthesia related to peripheral sensory polyneuropathy in 17% of patients.[157,160,161]

Interestingly, both clinical signs and subjective symptoms resulting from chemotherapeutic toxicity are correlated with the cumulative dose of cisplatin, with a higher incidence of ototoxicity, neurotoxicity and gonadal toxicity as well as arterial hypertension in patients who had been given cisplatin >400 mg/m^2 in total.[157]

Long-term survivors of testicular cancer have a ≥2-fold risk of developing cardiovascular disease.[163] Cardiovascular risk factors such as elevated serum cholesterol levels or arterial hypertension after chemotherapy are found in 15% of patients, even in analyses normalised to individual risk factors such as age and cigarette smoking.[164] Another study showed a 7-fold increased risk for coronary heart disease compared with normal population.[165] With more subtle diagnostic measures, such as Doppler echocardiography for left ventricular relaxation abnormalities, patients at risk might be identified and prophylactically treated.

Because chemotherapy is directly toxic to the germinal epithelium, loss of fertility after chemotherapy is another relevant adverse effect for germ cell tumour patients.[161,166,167] Azoospermia is present in all patients during treatment, but sperm production reinitiates 2 years after treatment in 50% of patients and 5 years after treatment in 80%.[168] Again, cumulative cisplatin dose is the most important prognostic factor and inversely correlated with fertility after treatment.[166] Sperm cryopreservation is generally recommended for all patients, including those with subfertile sperm counts at the time of diagnosis.

Secondary malignancies are a rare but serious complication after treatment with cisplatin-containing combination therapy, radiation,[165,167] and/or etoposide. The latter is associated with secondary leukaemia, which occurs in almost 0.5% of patients with a total dose of etoposide <2 g/m^2 and in up to 2% of patients receiving higher doses of etoposide.[169,170] The overall risk of developing a secondary malignancy is 2- to 3-fold higher than the overall risk for the general population.[171,172]

5. Conclusion

Much has been achieved in the treatment of testicular cancer and the ultimate goal of oncological therapy, namely tumour-free survival, has been reached for almost all patients with early-stage TGCT and for the majority with advanced disease. Nevertheless, patients with advanced disease have a poor prognosis, and there are several commonly made mistakes that lead to unnecessary treatment failures. First of all, a complete staging procedure for patients with advanced disease includes a diagnostic CT or MRI scan of the brain. Cisplatin should not be substituted with carboplatin in the absence of absolute contraindications. Because dose intensity is a crucial factor for good treatment results, neither the dosage of chemotherapeutic agents nor the number of therapeutic cycles should be reduced, and treatment intervals should not be prolonged in the absence of severe adverse effects. In addition, the sequence of therapeutic measures must be correctly set; orchiectomy should be performed prior to further treatment, except in patients with life-threatening metastatic disease. Finally, 'poor prognosis' patients should be sent to specialised centres for treatment to ensure an optimal standard of care.

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