Treatment of germ cell tumors – update 2006
C. Kollmannsberger¹, F. Honecker² & C. Bokemeyer²

¹Division of Medical Oncology, British Columbia Cancer Agency–Vancouver Cancer Centre, Vancouver, Canada; ²Department of Medical Oncology, Hematology, Pneumology, and Bone Marrow Transplantation, University Medical Center Eppendorf, Hamburg, Germany

introduction
Testicular cancer is considered a malignancy with a high cure rate even in patients with metastatic disease. Treatment strategies are based on the extent of the disease and prognostic factors and require cooperation of medical specialists such as medical oncologists, radiation oncologists and urologic surgeons. Today, cure rates of 95–99% for patients with early stage testicular cancer and 50–90% for patients with widely metastatic disease are achievable. While there are different treatment options for early stage disease, cisplatin-based combination chemotherapy with or without resection of residual masses remains the therapeutic mainstay for patients with metastatic disease. Three or four cycles of BEP (Bleomycin, Etoposide, Cisplatin) are given for patients with either a good and intermediate or a poor prognosis according to the International Germ Cell Consensus Classification Group (IGCCC) classification, respectively [1]. Four cycles of EP (etoposide, cisplatin) are an acceptable alternative to three cycles of BEP for good prognosis patients [2, 3].

Due to these excellent treatment results, testicular cancer research in recent years has mainly focused on two areas: on the one hand on minimizing toxicity while maintaining efficacy and evaluation of treatment-related long-term toxicity and on the other hand on the evaluation of new therapeutic options for patients with poor prognosis and cisplatin resistance. This also involves experimental work on the mechanisms of chemotherapy response and resistance in this disease. This review will focus on the most relevant findings provided in these fields within the most recent years.

molecular basis of the chemotherapy sensitivity and resistance of germ cell tumours
Despite various studies, no uniform hypothesis has been developed to explain the exquisite chemosensitivity of most germ cell tumors (GCTs) as well as the chemoresistance of the minority of malignant GCT. Multiple factors on different cellular levels seem to play a role in the induction of cell death following cisplatin-based chemotherapy, but the knowledge about the molecular basis of the development of chemoresistance is still poorly understood.

Cisplatin is believed to kill cells through interaction with the DNA, mainly by the formation of various DNA adducts, which lead to the initiation of programmed cell death (apoptosis) [4]. The tumor cell can escape the initiation of apoptosis on several levels.

Cisplatin can be inactivated by changes in the level of thiol-containing cell compounds such as glutathione or metallothionein or can be exported out of the cell by several export pumps, even before it reaches the DNA. A number of studies, predominantly done in cell lines and xenograft models, have suggested a correlation between glutathione and metallothionein levels and cisplatin resistance as well as between various export pumps, such as the ATP-binding cassette (ABC) transporters and the lung resistance protein, and cisplatin resistance [5–9]. However, validation on clinical tumor samples is lacking.

Cisplatin-induced DNA damage can be repaired, predominantly by the so-called ‘nuclear excision repair (NER) pathway’ prior to the activation of the apoptotic cascade. Investigations of the role of the NER, which is thought to be the most important DNA repair mechanism for cisplatin-induced damage, indicate a low capacity of GCT cells for NER. The low intrinsic capacity of the NER demonstrated in GCT cell lines has been attributed to low levels of xeroderma pigmentosum complementation group A protein (XPA) and the NER protein ERCC1. Alternatively, it has been proposed that the DNA adducts could be concealed by testis-specific high mobility group (HMG)-box proteins preventing damage detection and repair by NER factors [6, 10–13]. The finding of a low NER capacity itself and the potential clinical relevance have not been confirmed in samples from patients with GCTs, yet it is conceivable that a low NER activity contributes to the overall chemosensitivity of GCTs.

The recognition of the critical DNA damage by mechanisms, which initiate apoptosis, can fail. A high level of wild-type p53 in GCTs has commonly been regarded as the biological explanation for GCT chemosensitivity [14–16]. Two recent studies investigating the role of p53 in refractory GCT, have demonstrated that p53 mutations are rare even after treatment, that these mutations are unlikely to be the cause for chemotherapy resistance and that the inactivation of p53 does not lead to a sensitivity change in vitro [17, 18]. These findings suggest that induction of apoptosis in testis cancer cells can be executed even independent from p53, which questions the previously suggested important role of p53 in cisplatin resistance. A high incidence of microsatellite instability (MSI) was found in samples of patients with refractory GCT [19]. In most refractory cases MSI was found in several loci whereas in unselected GCT only very few patients had a MSI and if, most of
them just in one locus. MSI in refractory GCT indicates that defects in DNA mismatch repair pathway may represent a clinically relevant resistance mechanism. The execution of apoptotic cell death may be prevented by anti-apoptotic signals or by defects of apoptosis effectors. Other proteins involved in the regulation of apoptosis, such as BAX, BCL-2, BCL-XL and others have also been investigated, but no single factor seemed to correlate with treatment response [20]. This indicates no role for anti-apoptotic regulation downstream of the initiation of apoptosis in chemotherapy resistance of GCT.

Genetic analyses regarding chemotherapy resistance in clinical material of GCT patients are very rare. Specific genomic amplifications have been suggested to be related to chemoresistance of GCT, including high level amplifications at 1q31-32, 2p23-24, 7q21, 9q22, 9q32-34, 15q23-24, and 20q11.2–12 [21]. More investigation in GCT-chemotherapy-sensitivity may help to further improve treatment strategies in particular for patients with poor prognosis disease.

**Stage I Seminoma**

Approximately 75–80% of all patients with seminomas present with stage I disease. Without any further adjuvant treatment, approximately 15–20% of these patients will subsequently relapse but overall these patients exhibit an excellent prognosis with stage I disease. Without any further adjuvant treatment, stage I seminoma appears feasible and safe. Adjuvant radiation with 20 Gy to the para-aortic (± iliac) lymph nodes has been traditionally used as an adjuvant treatment for stage I patients based on studies which confirmed a majority of relapses in the retroperitoneal space. While this is a highly effective therapy [22], 80–85% of patients will undergo unnecessary treatment with the potential risk of severe late toxicities [23]. This led to several new initiatives to minimize or omit adjuvant therapy in stage I seminomas patients. The Medical Research Council (MRC) conducted 2 consecutive trials, the first comparing radiation with 30 Gy to radiation with 20 Gy (TE18) and the second comparing radiation with 20 or 30 Gray (Gy) to one cycle of carboplatin (TE19) [24, 25].

TE18 was designed as a non-inferiority trial aiming to exclude a 4% difference in relapse rate. 625 patients were randomized and after a median follow-up of 61 months (range 1 to 84 months) 87% of the relapses were diagnosed within the first two years, and 98% of the relapses were detected within 5 years. Disease-specific survival was 100% after a median follow-up of 60 months (Table 2). Surveillance is a clearly established option for stage I seminoma patients.

With cure rates approaching almost 100% for stage I seminoma, a risk adapted strategy appears to be an enticing approach. Two main risk factors, invasion of the rete testis and tumor size ≥4 cm, have been described for stage I seminoma patients with a relapse risk of approximately 35% if both factors are present [28]. These two risk factors were incorporated into a risk adapted strategy tested in a Spanish trial, in which 100 patients without risk factor were managed with surveillance whereas patients with one (n = 164) or both (n = 50) risk factors received 2 cycles of adjuvant carboplatin at a dose of AUC 7. Carboplatin was well tolerated with only 8% of patients experiencing grade 3 or 4 toxicity. Relapses were observed in 6% of the surveillance patients and 3.3% of the patients with risk factors. All relapsed patients were successfully salvaged with cisplatin-based combination chemotherapy. Median follow-up of the current study was only 34 months, which makes the definite appraisal of the results still difficult. However, similar results with relapse rates of 2–4% were reported after a median follow-up of 5–6 years in phase II studies with 2 cycles of adjuvant carboplatin for stage I seminoma (Table 1). Although these studies did not incorporate stratification by risk groups, no relapses have been reported beyond 3 years within these studies [26]. Based on these results, a risk adapted strategy in stage I seminoma appears feasible and safe.

**Late Toxicity**

With the high cure rate in testicular cancer patients, late toxicity has become a significant issue for these rather young patients. Radiation therapy has been traditionally used as an adjuvant treatment for stage I seminoma and as a curative therapy for stage II A/B seminomas. Equally effective appearing chemotherapy approaches are now emerging for these patients as described above. This makes the evaluation and assessment of long-term toxicity of each treatment option mandatory. Late toxicity may not only impair the quality of life of patients with malignant germ cell tumors, but therapy-related malignancies may also compromise their very good prognosis. A summary of the available data on the incidence of secondary malignancies to date, with treatment periods ranging from 1930 until 1995, generally indicates a two- to three-times
greater increased risk for developing therapy-related solid malignancies following therapy for testicular cancer [29]. The interpretation of these data is difficult due to the large variation of treatment during the time periods within these patients were diagnosed and treated. Some studies had already started in the 1930s or 1940s and had a follow-up extending only to the first half of the 1980s. Other studies, published more recently, included the treatment period up to the second half of the 1980s, thus reporting on a time period in which indications as well as doses and radiation techniques were already closer to the current practice. The different lengths of median follow-up of these studies ranging from 5.1 to 15.4 years must also be taken into account when interpreting the results.

When investigating the various treatment forms, radiation therapy appears to increase the risk for developing therapy-related solid tumors by a factor of two to three as compared to the general population. Two recent studies have confirmed these results. Amongst 40 576 1-year testicular cancer survivors Travis et al. observed 2285 second solid cancers [30]. Ten-year testicular cancer survivors treated with radiotherapy, chemotherapy or both were found to have a 2-fold, 1.8-fold and 2.9-fold increase in risk for secondary solid cancers after radiotherapy, chemotherapy or both, respectively. After 40 years, seminoma patients diagnosed at age 35 had a projected cumulative risk of 36% for developing a solid cancer as compared to 23% for the general population. Similar results of a 2–3-fold increase in risk were reported by Zagars et al. [23].

In recent years cardiovascular morbidity has been intensively investigated as a potential long term complication in cisplatin-based chemotherapy-treated patients. Cisplatin-based chemotherapy appears to induce both acute and long-term cardiovascular changes. Nuver et al. reported increased von Willebrand factor levels and an increase in the intima thickness of the carotid artery as signs of chemotherapy-induced vascular toxicity [31]. Meinardi observed an increased incidence of major cardiac events and an increased incidence of coronary artery disease in long-term survivors of metastatic testicular cancer [32]. Amongst 87 patients 6% experienced a myocardial ischemia and amongst 62 chemotherapy patients who underwent testing for their cardiovascular risk profile as part of the study, 39% had hypertension, 79% had hypercholesterolemia, 22% had microalbuminuria and 25% still experienced Raynaud’s phenomenon. Hypertension and hypercholesterolemia were significantly more frequent in chemotherapy-treated patients as compared to stage I patients, who had never received chemotherapy. These results were now confirmed by larger studies. Within a case-control study including 1814 Norwegian long-term survivors, chemotherapy-treated patients had increased odds for hypertension with approximately 50% of patients developing hypertension on follow-up [33]. High cumulative cisplatin doses (>850 mg) also appear to be associated with a higher body-mass-index and obesity. Amongst 2512 5-year survivors the risk for myocardial infarction after 4 cycles of PVB (cisplatin, vinblastine, bleomycin) was 1.9-fold increased [34]. Four cycles of PEB were associated with a 1.5-fold increase in cardiovascular risk, but no increase in the number of myocardial infarctions. This lack of an increase in myocardial infarctions may be due to the somewhat shorter follow-up of REP patients or due to the fact that vinblastine may cause additional effects on the autonomic cardiac nervous system [35]. Based on these results, patients should be monitored during long-term follow-up for cardiovascular risk factors and the development of hypertension, hypercholesterolemia and arteriosclerosis.

Despite the statistically significantly increased risk for long-term side effects, it is clear that the remarkable success in testicular cancer therapy far outweighs the risk for long-term toxicity. It can be assumed that modern treatment strategies including lower radiation doses, modified radiation fields and limited chemotherapy cycle numbers and doses will have a lower impact on long-term treatment-related side effects. However, even a low number of therapy-related long-term complications should encourage the search for equally effective but less toxic therapies.

### treatment of patients with cisplatin-refractory germ cell cancer

Various chemotherapeutic agents have been evaluated in intensively pretreated or cisplatin-refractory patients. However, as single agents, only orally administered etoposide, paclitaxel, gemcitabine and most recently oxaliplatin have been shown to

---

**Table 1.** Phase II studies with 2 cycles of carboplatin as adjuvant treatment in stage I seminoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number patients</th>
<th>Dose</th>
<th>Relapse rate</th>
<th>Median follow-up</th>
<th>Cause-specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner [41]</td>
<td>2002</td>
<td>108</td>
<td>400 mg/m²</td>
<td>1.8%</td>
<td>60</td>
<td>100%</td>
</tr>
<tr>
<td>Oliver [42]</td>
<td>2001</td>
<td>146</td>
<td>AUC 7</td>
<td>0.7%</td>
<td>52</td>
<td>100%</td>
</tr>
<tr>
<td>Reiter [43]</td>
<td>2001</td>
<td>107</td>
<td>400 mg/m²</td>
<td>0%</td>
<td>74</td>
<td>100%</td>
</tr>
<tr>
<td>Dieckmann [44]</td>
<td>2000</td>
<td>32</td>
<td>400 mg/m²</td>
<td>0%</td>
<td>48</td>
<td>100%</td>
</tr>
<tr>
<td>Nost [45]</td>
<td>1998</td>
<td>36</td>
<td>400 mg/m²</td>
<td>0%</td>
<td>52</td>
<td>100%</td>
</tr>
<tr>
<td>Krege [46]</td>
<td>1997</td>
<td>43</td>
<td>400 mg/m²</td>
<td>0%</td>
<td>28</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Table 2.** Surveillance in stage I seminoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Number patients</th>
<th>Median follow-up (months)</th>
<th>Relapse rate</th>
<th>Cause-specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horwich 1992 [47]</td>
<td>103</td>
<td>62</td>
<td>16.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Daugaard 2003 [27]</td>
<td>394</td>
<td>60</td>
<td>17.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Choo 2005 [48]</td>
<td>88</td>
<td>121</td>
<td>19.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Warde 2005 [49]</td>
<td>421</td>
<td>97</td>
<td>15.2%</td>
<td>99.7%</td>
</tr>
</tbody>
</table>
be active in refractory disease with selected patients achieving complete remissions. This has led to the evaluation of combination chemotherapy regimens such as gemcitabine/paclitaxel or oxaliplatin/gemcitabine, demonstrating the feasibility and activity of combination therapy in these heavily pretreated patients (Table 3). Achieving a high response rate in refractory patients is important since the induction of a remission may subsequently allow the resection of residual masses and may thus be a chance to still achieve long-term survival in selected patients [36].

The most favorable results have thus far been obtained with the combination consisting of gemcitabine and oxaliplatin in a prognostically very unfavorable patient population in two independent studies [37, 38]. Response rates of 32 and 46% were achieved. It is important to note, that all of the studies investigating combination chemotherapy regimens have reported patients with complete responses. Combination chemotherapy and, if possible, resection of residual masses, should therefore now be considered as a useful therapeutic option for patients in good performance status with a sufficient bone marrow reserve.

Three drug regimens, such as gemcitabine, oxaliplatin and paclitaxel or paclitaxel, gemcitabine and cisplatin are now being developed in clinical trials. Despite interesting preliminary response rates, these 3-drug combinations are still associated with frequent and substantial toxicity in these heavily pretreated patients resulting in a high number of dose/schedule modifications and early treatment termination [39, 40]. These studies may however lead to the development of a 3-drug combination regimen, which is entirely non-cross resistant to the standard cisplatin-based regimens currently used for germ cell cancer.

Novel molecular targets are now also being explored in germ cell cancer. Vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors are currently under investigation in patients with refractory disease, but no results are thus far available.

In conclusion, the management of testicular cancer has evolved to a risk adapted approach trying to balance treatment efficacy and acute and long-term toxicity within the individual decision making. The upcoming results of molecular studies may hopefully allow further refining of treatment approaches in this highly curable group of cancer patients.

### references


15. Lutzker SG. P53 tumour suppressor gene and germ cell neoplasia. APMIS 1998; 106: 85–89.


