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# Cisplatin-Based Chemotherapy of Testicular Cancer – two Decades After a Major Breakthrough

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**Key Words**
Testicular cancer · Germ cell tumor · Cisplatin · Chemotherapy

**Schlüsselwörter**
Hodentumor · Keimzelltumor · Cisplatin · Chemotherapie

**Summary**
Two decades ago the introduction of cisplatin-based combination chemotherapy has dramatically improved the prognosis of patients with metastatic testicular cancer. At present 3 cycles of cisplatin, etoposide and bleomycin are considered as standard treatment for good-risk metastatic disease. Outside of clinical trials patients in the intermediate and poor prognosis categories should receive 4 cycles of this standard regimen. Clinical trials currently evaluate the role of high-dose chemotherapy in first-line treatment of high-risk patients and in the salvage setting. Post-chemotherapy resection of tumor residuals remains an important part of therapy. Attention should be focused on long-term toxicity of therapy and the occurrence of late relapse.

**Zusammenfassung**
Vor zwei Jahrzehnten hat die Einführung cisplatinhaltiger Kombinationschemotherapie die Prognose von Patienten mit metastasiertem Hodentumor erheblich verbessert. Gegenwärtig werden 3 Zyklen Cisplatin, Etoposid und Bleomycin als Standardtherapie für Patienten mit prognostisch günstiger Metastasierung angesehen. Außerhalb von klinischen Studien sollten Patienten mit intermediärer und ungünstiger Prognose 4 Zyklen dieses Standardprotokolls erhalten. Klinische Studien untersuchen derzeit die Rolle der Hochdosischemotherapie als Ersttherapie für Hochrisikopatienten und bei rezidivierter Erkrankung. Die Resektion von Tumorresiduen nach Chemotherapie bleibt ein wichtiger Bestandteil der Therapie. Der langfristigen Toxizität der Therapie und dem Vorkommen von Spätrezidiven sollten Aufmerksamkeit geschenkt werden.

## Introduction

Testicular germ cell tumor is a relatively rare neoplasm, accounting for only 1–2% of malignancies in adult men [1]. However, testicular cancer is the most common solid tumor in the third and fourth decade of life. Presently, approximately 3,000 new cases per year are diagnosed in Germany. The incidence varies according to geographic area; it is highest in Scandinavia followed by Germany and New Zealand. Over the past five decades the incidence has doubled every 20 years.

## History of Chemotherapy

Around four decades ago testicular cancer was recognized as a chemosensitive tumor. Combination chemotherapy consisting of dactinomycin, methotrexate, and chlorambucil led to a 50% response rate in metastatic disease, and 5–10% of patients attained long-term disease-free survival [2]. Some improvement was achieved by using a combination of vinblastine and bleomycin; the cure rate rose to 25% [3]. However, the major breakthrough in the history of chemotherapy for testicular cancer was the discovery of cisplatin by Rosenberg and coworkers [4]. In early clinical trials cisplatin proved to be toxic with only modest activity in various solid tumors when used in heavily pretreated patients. Higby et al. [5] first evaluated the activity of cisplatin in pretreated testicular cancer patients, and reported 3 complete and 3 partial remissions in 11 patients.

In 1974 Einhorn and Donohue [6] added the experimental drug cisplatin to the established regimen of vinblastine and bleomycin. Patients received 4 courses of the combination cis-

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platin, vinblastine, and bleomycin followed by maintenance chemotherapy consisting of 0.3 mg/kg vinblastine monthly for 2 years. Of the first 47 patients 33 (70%) achieved complete response and an additional 5 (11%) were rendered disease-free by post-chemotherapy resection of residual masses [6]. This combined modality approach also was novel, and required urological and thoracic surgical expertise. A subsequent randomized trial demonstrated no benefit for maintenance therapy; the relapse rate after complete response to four cycles of induction chemotherapy was only 5% with or without maintenance vinblastine [7]. In Germany cisplatin-based chemotherapy for testicular cancer was introduced in 1979.

In 1980 Fitzharris et al. [8] documented the single-agent activity of etoposide in refractory testicular cancer. Thereafter, a randomized trial compared the combination of cisplatin 20 mg/m$^2$ (days 1–5) and bleomycin 30 mg (days 2, 9, 16) with either vinblastine 0.15 mg/kg (days 1, 2) or etoposide 100 mg/m$^2$ (days 1–5) as first-line treatment for metastatic testicular cancer [9]. In the etoposide arm there was a major reduction of neuromuscular toxicity. Moreover, in the worst prognostic subgroup there was a survival advantage for cisplatin, etoposide, and bleomycin (PEB). Since 1987 this combination has been used as standard first-line chemotherapy for metastatic testicular cancer.

Summarizing 5 early studies of ifosfamide in patients without pretreatment with cisplatin there was a response rate of 65%, a complete response rate of 20%, and a number of durable complete responses of 2.5–8 years [10]. In the setting of prior cisplatin-based chemotherapy the activity of ifosfamide was considerably lower with a 20% overall response rate and only a 1% complete response rate. Whereas ifosfamide is now a component of many salvage protocols, its role in first-line therapy of testicular cancer still has to be defined.

In the following sections current strategies and future perspectives for the treatment of testicular cancer are discussed. As nonseminomatous tumors and pure seminomas have a different biological behavior with consequences for treatment, both entities are presented separately.

## Nonseminomatous Germ Cell Tumor

*Adjuvant Chemotherapy*

The high activity of cisplatin-based chemotherapy in metastatic disease led to its evaluation in the adjuvant setting. Whereas patients with resected stage IIA/B testicular cancer (retroperitoneal lymph nodes less than 5 cm in diameter) develop recurrent disease in around 50% on surveillance, 2 cycles of standard chemotherapy almost always prevent relapse [11].

In recent years some investigators propagated adjuvant chemotherapy for high-risk stage I disease. Almost three quarters of patients with stage I disease belong to a low-risk group with a risk of relapse of less than 20%; these patients are set on a surveillance protocol with chemotherapy reserved for relapse. The remaining patients with high-risk features (histopathologic criteria) carry a risk of relapse of around 50%; 2 cycles of adjuvant chemotherapy reduce the recurrence rate to less than 5% [12].

*Chemotherapy for Metastatic Disease*

As an alternative to bilateral retroperitoneal lymph node dissection some investigators evaluated primary chemotherapy for stage IIA/B disease [12]. Approximately two thirds of patients achieve a complete response to 3 (to 4) cycles of standard chemotherapy. The remaining patients have to undergo post-chemotherapy resection of residual masses. Thus a considerable proportion of patients is spared the morbidity of a surgical intervention by this approach, but a relapse rate of around 10% is higher than for retroperitoneal lymph node dissection followed by adjuvant chemotherapy. Nevertheless, similar survival rates between 95 and 100% were reported for both treatment options [12].

Patients with retroperitoneal lymph node metastases greater than 5 cm in diameter, supradiaphragmatic lymph node involvement or visceral metastases undergo chemotherapy as first treatment modality. According to the International Germ Cell Cancer Collaborative Group (IGCCCG) patients are divided into 3 prognostic categories (table 1) [13]. Prognostic factors include the levels of the tumor markers human chorionic gonadotropin (HCG) and alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH) as well as rare tumor sites. In the large cohort of more than 5,000 patients of the IGCCCG study 56% of the patients belonged to the good-risk group with a 5-year survival rate of 91%. The intermediate-risk group comprised 28% of the cohort, and was characterized by a 5-year survival rate of 79%. The poor-risk group constituted 16% of the patients with a 5-year survival of only 48%.

As a randomized trial comparing 4 versus 3 cycles of standard chemotherapy in minimal and moderate disease according to Indiana University classification demonstrated no difference in response and survival rates, 3 cycles of PEB are currently considered as standard treatment for good-risk patients [14]. Recently, an EORTC/MRC phase III study comparing 3 versus 4 cycles of standard chemotherapy in IGCCCG good-risk patients confirmed the equivalence [15]. In poor-risk patients neither doubling of the cisplatin dose nor substitution of ifosfamide for bleomycin led to an improvement of outcome [16, 17]. Outside of clinical trials patients in the intermediate and poor-risk categories should receive 4 cycles of PEB.

There is some evidence that survival rates for patients in the intermediate and poor-risk categories improved during the cisplatin era. Substitution of etoposide for vinblastine, cumulative experience, advances in supportive care and treatment intensification have been discussed as contributory factors [18]. However, the role of dose-intensified therapy is difficult to define. The only randomized trial that compared PEB with a sequential dose-intensified regimen (BOP/VIP-B: bleomycin, vincristine, cisplatin/etoposide, ifosfamide, cisplatin-bleomycin) could not demonstrate a survival advantage for the experimental arm [19]. However, the lack of superiority of the BOP/VIP-B protocol might be due to its composition: the doses of etoposide (VP-16) and ifosfamide were 20–25% lower than in other VIP protocols. Furthermore, almost 50% of patients had moderate dose reductions. Recently reported retrospective studies suggested that treatment intensification might improve clinical outcome of poor-risk patients. For the cyclical protocol POMB/ACE (cisplatin, vincristine, methotrexate, bleomycin/ actinomycin D, cyclophosphamide, etoposide)

**Table 1.** International consensus classification for metastatic germ cell cancers

| Prognostic category | Seminoma | | Nonseminoma | | |
|---|---|---|---|---|---|
| | metastases | site | tumor marker | metastases | site |
| Good-risk | no non-pulmonary visceral metastases | any primary site | AFP < 1,000 ng/ml<br>HCG < 5,000 U/l<br>LDH < 1.5 × N* | no non-pulmonary visceral metastases | testicular/retroperitoneal primary site |
| Intermediate-risk | non-pulmonary visceral metastases | any primary site | AFP 1,000–10,000 ng/ml<br>HCG 5,000–50,000 U/l<br>LDH 1.5–10 × N* | no non-pulmonary visceral metastases | testicular/retroperitoneal primary site |
| Poor-risk | – | – | AFP > 10,000 ng/ml<br>HCG > 50,000 U/l<br>LDH > 10 × N* | non-pulmonary visceral metastases (bone, liver, brain) | mediastinal primary site |

*N = Upper limit of normal range.

a 3-year survival rate of 75% was reported for poor-risk patients compared to 50% in the IGCCCG study [20]. A German multicenter study performed a stepwise dose escalation of etoposide and ifosfamide in the PEI (cisplatin, etoposide, ifosfamide) protocol with stem cell support. A recent matched-pair analysis comparing high-dose PEI with standard-dose PEB or PEI demonstrated a significant survival advantage for first-line high-dose chemotherapy (3-year survival 80 vs. 61%, p = 0.02) [21]. In the United States a randomized trial currently compares 4 cycles of PEB with 2 cycles of PEB followed by 2 cycles of high-dose carboplatin, etoposide and cyclophosphamide in intermediate and poor-risk patients.

Nonseminomatous germ cell tumors in the intermediate and poor-risk categories are rare. Some studies demonstrated that referral to a specialist unit significantly improves survival [22, 23]. Moreover, a recent international study showed that treatment-related deaths were more frequent at hospitals that treated less than 5 cases compared with centers that treated 20 or more patients (13 vs. 3%) [19].

*Post-Chemotherapy Surgery*

After the end of chemotherapy a considerable proportion of patients shows residual masses at CT scans. These residual masses consist of necrosis/fibrosis, mature teratoma or viable cancer [24]. In two large series necrosis/fibrosis was found in 45%, mature teratoma in 42% and viable cancer in 13% of retroperitoneal tumor residuals [25, 26]. Resection of tumor residuals containing necrosis/fibrosis is only a diagnostic procedure. In contrast, resection of mature teratoma or viable cancer provides a therapeutic benefit. For almost two decades it has been standard at many institutions to give 2 further cycles of chemotherapy to patients with resected viable cancer, although there was no consensus whether chemotherapy should be applied according to the induction protocol or an alternative regimen. Recently, a retrospective international study demonstrated that additional chemotherapy in patients with resected viable cancer improved progression-free survival but did not have a significant impact on overall survival [27].

Approximately one third of patients shows tumor residuals in multiple anatomic sites, for example in the retroperitoneum and the lungs [28]. Some investigators advocate complete resection of all tumor residuals if technically feasible [29]. However, in an international study 48 of 54 patients (89%) with necrosis at retroperitoneal lymph node dissection had the same favorable histology at thoracotomy [30]. These data suggest that the benefit of a second or third surgery is low if there is necrosis/fibrosis in the resected retroperitoneal mass. Because of the high predictive value of the histology in the retroperitoneal space retroperitoneal lymph node dissection should usually precede thoracotomy.

*Salvage Treatment*

Patients who need salvage chemotherapy for refractory or recurrent disease carry a relatively poor prognosis. After conventional salvage treatment (cisplatin-ifosfamide-based chemotherapy with either vinblastine or etoposide) only 20–30% of patients attain long-term disease-free survival [31, 32]. A recent study identified the following unfavorable prognostic factors after conventional salvage treatment: incomplete response to first-line chemotherapy, time to progression less than 2 years, high levels of tumor markers (HCG > 100 U/l or AFP > 100 U/ml) [33]. Patients with all 3 poor-risk features constituted one quarter of the entire group. Prognosis was dismal in this subgroup, no patient was alive 3 years after the start of salvage treatment. The remaining three quarters of patients with no more than 2 poor-risk factors attained a 5-year survival rate of around 50%.

As high-hose chemotherapy with autologous bone marrow rescue achieved durable responses in around 15% of heavily pretreated patients (third-line or later) in early studies [34], this treatment option is now increasingly used as first salvage treatment. In a recent study that included 49 patients with first relapse, 25 patients (51%) were continuously disease-free after a minimal follow-up of 12 months after high-dose chemotherapy [35]. However, patients with extragonadal primaries, who carry a less favorable prognosis than patients with testicular tumors, were excluded from this study. Recently, a matched-pair

analysis comparing conventional chemotherapy and high-dose chemotherapy at first relapse, showed a small but significant survival advantage for patients receiving high-dose chemotherapy [36]. A European study prospectively compares conventional and high-dose chemotherapy for patients with favorable prognostic features at first relapse; patient accrual is ongoing. Recently, a German phase III trial started that includes patients at first and subsequent relapses. One arm consists of 3 cycles of standard salvage therapy followed by 1 cycle of high-dose carboplatin, etoposide, and cyclophosphamide. Patients randomized to the other arm receive 1 cycle of standard salvage therapy followed by 3 cycles of high-dose carboplatin and etoposide.

Despite the encouraging results in some studies, high-dose chemotherapy for testicular cancer should be still regarded as an investigational approach. This treatment should be given only at specialist centers and only in the setting of a clinical trial.

As a considerable proportion of patients develops relapse after high-dose chemotherapy, the evaluation of new drugs still plays a major role in clinical investigations of testicular cancer. Recent studies identified paclitaxel and gemcitabine as active agents in testicular cancer with response rates of around 20% in heavily pretreated patients [37, 38]. In clinical trials paclitaxel has been already incorporated in first-line and salvage chemotherapy protocols. German phase II studies currently evaluate the activity of bendamustine and oxaliplatin in heavily pretreated patients.

Late relapses of testicular cancer are defined as recurrences after a relapse-free interval of more than 2 years after discontinuation of primary therapy. Unselected patients appearing disease-free at 2 years have a cumulative risk of late relapse of about 4% at 10 years [39]. Patients with a high tumor burden at the start of primary chemotherapy carry a substantially higher risk for late relapse than patients with a small-volume disease. Late relapses are often resistant to chemotherapy. However, surgery can cure patients with localized resectable disease.

## Seminoma

*Early Stages*

Seminomas are characterized by a less aggressive biological behavior than nonseminoma and predominant lymphogenous dissemination. Approximately 85% of patients present with clinical stage I disease. As almost 20% of stage I patients have occult retroperitoneal lymph node metastases, prophylactic para-aortic radiotherapy is recommended as standard treatment [40]. As an alternative to radiotherapy, adjuvant chemotherapy with carboplatin, a less toxic platinum compound than cisplatin, is currently evaluated in clinical trials. One study group propagates surveillance for stage I seminoma patients with radiotherapy or chemotherapy reserved for relapse [41].

Treatment of stage IIA/B seminoma is also a domain of radiotherapy [41]. Around 15% of stage IIB patients (retroperitoneal lymph nodes between 2 and 5 cm in diameter) develop a relapse outside of the irradiated field; a high proportion of these patients can be successfully salvaged by cisplatin-based chemotherapy. Prognosis of stage I and IIA/B seminoma patients is excellent with long-term survival rates between 95 and 100%.

*Advanced Stages*

Patients with stage IIC/D seminoma (retroperitoneal lymph nodes greater than 5/10 cm) develop relapses after radiotherapy in a proportion of around 50%. There is now a consensus that these patients should receive cisplatin-based chemotherapy as first-line therapy, as well as patients with supradiaphragmatic lymph node involvement or visceral metastases [41]. Patients with lymph node and/or lung metastases attain long-term disease-free survival rates of around 90%. The small number of patients with non-pulmonary visceral metastases belongs to the intermediate-risk group according to IGCCCG criteria with a cure rate between 70 and 80%. A German multicenter trial currently compares the efficacy of a combination of etoposide, ifosfamide and cisplatin with single agent carboplatin in advanced seminoma. Post-chemotherapy resection of residual masses plays a minor role in seminoma compared with nonseminoma. One study group recommends resection of masses greater than 3 cm [42]. Other investigators prefer a policy of close observation [43].

## Late Toxicity

As patients cured from testicular cancer expect an additional 50 years to live, late toxicity is of major interest. Recently, we described a remarkable storage of platinum in chemotherapy-treated long-term survivors of testicular cancer [44]. At 5.3–16.8 years after chemotherapy urinary platinum excretion and serum platinum levels were 100 to 1,000 times higher in patients than in unexposed controls.

In a study that included 90 patients with a median follow-up of 58 months after chemotherapy, most frequent symptomatic toxicities were Raynaud's phenomenon in 30% of patients, ototoxicity in 21%, and peripheral neuropathy in 17% [45]. These toxicities were significantly more frequent in patients who had received a cumulative cisplatin dose higher than 400 mg/m$^2$.

Fertility is another important issue. A recent study documented that spermatogenesis is already impaired in men with testicular cancer before orchiectomy [46]. The most likely explanation is preexisting impairment of spermatogenesis in the contralateral testis in men with testicular cancer. Cisplatin-based chemotherapy has an additional adverse effect on spermatogenesis which is only in part reversible [47]. Normospermia before chemotherapy was recognized as favorable prognostic factor for recovery of spermatogenesis after chemotherapy. Patients receiving a cumulative cisplatin dose higher than 400 mg/m$^2$ had unfavorable prospects of fertility. Sperm banking should be offered to testicular cancer patients prior to start of chemotherapy.

Presently, there is no consensus whether chemotherapy for testicular cancer leads to an increase of cardiovascular risk. Some studies described elevated serum cholesterol levels after cisplatin-based chemotherapy, whereas other investigators could not confirm this finding [48]. Another question is whether cisplatin-based chemotherapy leads to an increase of

second cancer risk. In animal models, platinum causes solid tumors, as well as leukemia. Travis et al. [49] described a significantly elevated risk of second malignant neoplasms for more than two decades following radiotherapy or chemotherapy for testicular cancer. This study could not clarify the role of cisplatin. However, a recent case-control study demonstrated an increased risk of leukemia after platinum-based chemotherapy for ovarian cancer [50]. Moreover, in testicular cancer the use of etoposide adds to the risk of leukemia.

## Conclusions

Two decades after introduction of cisplatin-based chemotherapy for testicular cancer many questions have been answered by clinical studies. Present issues include improvement of therapy for poor-risk metastatic disease, salvage chemotherapy strategies and indications for resection of residual masses after chemotherapy. Attention should be also focused on long-term toxicity and the occurrence of late relapse.

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