Germ Cell Tumors in Children and Adolescents

Gabriele Calaminus, Catherine Patte

Introduction
Germ cell tumors (GCTs) constitute a highly heterogeneous group of tumors that significantly varies with respect to site, clinical presentation, histology and biology. This heterogeneous clinical presentation requires a multimodal treatment that includes the paediatric oncologist in cooperation with the appropriate surgical disciplines (paediatric surgeon, urologist, gynecologist, thoracic surgeon, and neurosurgeon) and the radiotherapist. During the past two decades, a dramatic improvement of the prognosis of malignant GCTs both in the adult and in the paediatric population has been achieved. This progress can mainly be attributed to national and international cooperative therapeutic protocols that utilized cisplatinum-based combination chemotherapy as part of a multimodal therapeutic approach. The following chapters summarize the rapid development during recent years, and describe what should be considered up-to-date therapy of paediatric GCT.

Epidemiology
Germ cell tumors may become clinically apparent in all age groups, ranging from the fetal period to adulthood. Among children younger than 15 years, GCTs are comparatively rare and account for approximately 3-4% of all diagnoses enrolled onto epidemiologic registries. During childhood, the majority of GCTs present at nongonadal sites close to the body axis, e.g. the sacrococcygeal region, mediastinum or the pineal gland. Two incidence peaks can be observed within the paediatric tumors. The first peak includes teratomas (in neonates) and yolk sac tumors (during infancy and early childhood) that predominantly arise in the sacrococcygeal region, testis and less frequently the mediastinum or retroperitoneum.

In the second decade of life another rise of incidence can be seen that is due to the gonadal, mediastinal and CNS tumors. Histologically, these tumors resemble germinoma (syn.: seminoma, dysgerminoma) or nonseminomas including embryonal carcinoma, choriocarcinoma and yolk sac tumor. Ovarian cystic teratoma (dermoid cyst) most commonly occur during adolescence and comprise a distinct clinical entity that is characterized by a specific biology and benign clinical behavior.

Histologic Classification of Germ Cell Tumors
GCT are characterized by a profound heterogeneity of their histologic differentiation. They are classified according to the WHO-classification of testicular, ovarian and intracranial tumors respectively (Table 1). As intra-tumor heterogenity may be subtle, the initial diagnostic work-up should include the evaluation by a pathologist experienced in GCT histology in order to achieve a standardized and reliable histopathologic diagnosis and grading (Table 1).

According to the holistic concept of Teilum GCT arise from totipotent primordial germ cells which are capable of embryonic and extraembryonic differentiation. In contrast to testicular GCT of adult patients paediatric GCT do not develop from carcinoma in situ.

In most patients, the response to the different therapeutic modalities can be predicted from the histologic appearance and the tumor marker profile (Table 2). About 25% of all paediatric GCT present as tumors with more than one histologic type. In this situation therapy and prognosis depend on the component with the highest malignancy (1).
Biology

Molecular studies of GCT revealed that gonadal and nongonadal GCT share a common cellular origin (2). While no consistent correlation between cytogenetic aberration and primary site of the tumor has been observed, it is apparent that histology (teratoma vs. malignant GCT) and age (pre- vs. postpubertal) both significantly correlate with distinct genetic profiles (3). More than 80% of malignant testicular GCTs of young males display a distinct and specific chromosomal aberration, the isochromosome 12p (4). The remaining isochromosome 12p - negative tumors frequently show amplification of 12p (homogeneously staining regions or tandem repeats), and candidate genes have recently been identified in this region.

In contrast to adult patients, in malignant GCT of children younger than 10 years an isochromosome 12p has rarely been found. On the other hand, aberrations at chromosomes 1, 6, and 20 and the sex chromosomes have been found frequently (4).

Lastly, virtually all pure teratomas are cytogenetically normal. However, cystic teratoma

<table>
<thead>
<tr>
<th>Table 1: Histologic classification of germ cell tumors according to the World Health Organization (WHO)</th>
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<tr>
<td><strong>Synonyms</strong></td>
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<tr>
<td><strong>1. Seminoma (SE)</strong></td>
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<td><strong>2. Yolk sac tumor (YST)</strong></td>
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<td><strong>3. Embryonal carcinoma (EC)</strong></td>
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<td><strong>4. Choriocarcinoma (CHC)</strong></td>
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<tr>
<td><strong>5. Teratoma (TER)</strong></td>
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<tr>
<td><strong>5.1. Mature</strong></td>
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<tr>
<td><strong>5.1.1. Solid</strong></td>
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<td><strong>5.1.2. Cystic</strong></td>
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<td><strong>5.2. Immature (IT)</strong></td>
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<td><strong>5.3. with malignant transformation</strong></td>
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<td><strong>5.4. Monodermal</strong></td>
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<tr>
<td><strong>6. Tumors with mixed histology (MGCT)</strong></td>
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<tr>
<td><strong>7. Spermatocytic Seminoma (SS)</strong></td>
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<td><strong>8. Polyembryoma (POLY)</strong></td>
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<th>Table 2: Biological characteristics of the histologic germ cell tumor subentities</th>
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<td></td>
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<tr>
<td>Seminoma/germinoma</td>
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<tr>
<td>Embryonal carcinoma</td>
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<tr>
<td>Yolk sac tumor</td>
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<tr>
<td>Choriocarcinoma</td>
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<tr>
<td>Teratoma, mature/immature</td>
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of the ovary may present with isodisomic karyotype, consistent with their origin from postmeiotic germ cells.

**Diagnosis**

In general, GCTs tend to occur as indolent masses, and clinical symptoms are mostly related to local dysfunction by tumor growth. If a GCT is suspected on the basis of the clinical assessment, a defined program of clinical, radiographic, and laboratory investigations has to be followed in timely fashion. The radiographic procedures must be performed with respect to tumor site and potential ways of tumor dissemination.

**Tumor markers**

Depending on their histologic differentiation GCT tend to secrete the tumor markers AFP and/or HCG/ß-HCG (Table 2). These facilitate clinical diagnosis in tumors that present at typical sites (5). It is important to note that in contrast to other reports, this series of normal neonates in infants has demonstrated that in a significant percentage of healthy children, the AFP does not decline to the normal range of adult patients before the end of the second year of live (6). Therefore, in the first two years of life, only AFP levels significantly above the age-related normal value can be regarded as diagnostic for a secreting GCT.

In general, the tumor marker profile is highly specific for the histologic differentiation of the tumors (Table 1). In CNS GCT it is frequently observed that markers maybe elevated at different levels in CSF and serum. Therefore measurement at diagnosis in both compartments is mandatory.

About 20% of germinoma may secrete the Placenta-like Alkaline Phosphatase (PLAP), which can be used also as additional diagnostic tool, if elevated.

**Diagnostic imaging**

In most patients with extracranial tumors, the initial radiographic assessment of the tumor will be made by ultrasound. During ultrasound, the tumor should be measured in three dimensions, and in addition, the abdomen and the lymph nodes should be screened for metastases. The next step will be to perform CT, preferably MRI scans of the tumor.

**Laboratory studies (pre-treatment)**

In addition to the tumor markers AFP and ß-HCG, serum LDH has proven a prognostic marker in adult patients with GCTs. In germinomas, the Placenta-like Alkaline Phosphatase (PLAP) can be measured in the serum and may then serve as a marker of treatment response during follow-up. In addition to the routine blood tests and tumor markers specific attention should be given to the renal function (creatinine clearance, urine electrolytes), as several cytotoxic agents such as platinum-compounds and ifosfamide may interfere with renal function.

**Surgery**

If the initial radiographic assessment uncovers infiltration into adjacent organs and/or metastases, up-front chemotherapy followed by delayed tumor resection is recommended, as preoperative chemotherapy will facilitate complete resection on delayed surgery (7). For most sites except the liver and the retroperitoneum, tumor marker measurement in combination with imaging allows for a clinical diagnosis. In equivocal cases (i.e. non-diagnostic markers, hepatic or upper retroperitoneal tumors), a diagnostic biopsy is recommended.

If the radiographic assessment indicates a localized tumor without metastatic spread, a primary tumor resection constitutes the treatment of choice, except in CNS, as this region bears specific risks of surgical morbidity. In patients with tumor residues after initial tumor resection, 2nd look surgery is essential to achieve secondary complete resection. This is also the case in malignant non-germinomatous CNS GCTs. Finally, surgery of metastases is not indicated unless they show insufficient response to chemotherapy (8).

**Cisplatinum-based Chemotherapy**

The modern era of GCT chemotherapy began in the mid 1970s with the identification of the efficacy of cisplatinum in testicular GCT. In 1977, Einhorn and Donohue reported a complete response rate of 85% in patients with metastatic testicular GCT with a combination of cisplatinum, vinblastin and bleomycin (PVB) in adjunct to tumor resection (9). Most importantly, in contrast to previously reported regimen with only vinblastin and
bleomycin, the overall good response was also translated into durable remissions.

Nevertheless, relapses or refractory cancers – although rare – established the need for second line therapies. Etoposide soon emerged as an active drug with a single-agent efficacy superior to vinblastin. On the other hand, the use of etoposide can be associated with therapy-related leukemias in approximately 1-2% of patients. In addition, the efficacy of ifosfamide in cisplatinum-refractory GCT has been documented. The combination of cisplatinum with etoposide and ifosfamide for recurrent testicular GCT results in a 30% durable remission rate and can now be considered standard relapse treatment. These observations have initiated studies that included etoposide and/or ifosfamide into the first line treatment of GCT.

In relapsing and refractory GCTs, the therapeutic value of high dose chemotherapy with autologous stem cell transplantation has been investigated. These analyses have shown only limited efficacy in prognostically unfavorable tumors such as cisplatinum-resistant, mediastinal GCTs with high ß-HCG are multiple relapses. Nevertheless, in some patients introduction of high dose chemotherapy into first-line treatment of high-risk tumors may be beneficial.

Development of Cooperative Protocols for Paediatric GCTs The first published trial was conducted by the US Childrens Cancer Group (CCG) and included 54 children with malignant nonseminomatous GCT. Patients underwent initial tumor resection followed VAC+PVB chemotherapy over a two year period, second look resection four months after diagnosis and irradiation in case of residual tumor. Fifteen of 20 evaluable patients with ovarian nonseminomatous GCT achieved a continuous clinical remission. The prognosis of children with nongonadal GCT was worse - ten of 18 evaluable patients achieved CR - but still encouraging compared to all other previous studies.

The analysis of the consecutive CCG protocol included 93 children. Patients with ovarian GCTs had a better prognosis (4 year EFS 63%) than children with nongonadal GCTs (4 year EFS 42%) (10). This difference was mainly attributed to a higher rate of incomplete tumor resections in nongonadal tumors.

In the consecutive US Intergroup protocol, a watch-and-wait policy was followed in stage I testicular GCTs. Intermediate risk patients (testicular stage II, ovarian and nongonadal stage I-II) received four cycles cisplatinum, etoposide, and bleomycin (reduced to one infusion per cycle compared to three infusions in corresponding adult regimens). Furthermore, in high risk patients (stage III-IV), the therapeutic impact of cisplatinum dose intensification at 200 mg/m²/cycle was evaluated. The analysis of both gonadal and nongonadal GCTs revealed that higher doses of cisplatinum may result in higher response and complete remission rates (approximately 9% benefit), however at a significantly higher renal and auditory toxicity. More recent investigations of this study group also stated that amifostine protection during cisplatinum therapy at escalated doses gives no significant benefit with regard to ototoxicity has been demonstrated, and amifostine therapy was associated with significant electrolyte imbalances, particularly hypocalcaemia (11).

The analysis of different chemotherapy regimens administered in the British UKCCG GC I and GC II protocols also demonstrated the high therapeutic efficacy of platinum-based regimens such as BEP or JEB (carboplatinum (600 mg/m²/cycle), etoposide, bleomycin) that resulted in a five year EFS of 57% and 87% in nongonadal GCTs (12). The recent analysis of the UKCCG GC II study underscores the high efficacy of the JEB regimen, that resulted in a 5-year EFS of 88% with a favorable toxicity profile (13).

The French study group reported 35 children with ovarian and nongonadal advanced stage GCTs that were treated with a VAC+PB regimen, and a two year survival of 63% was achieved (14). The French cooperative protocol TGM 85 used a similar chemotherapeutic approach, and in the consecutive TGM 90 protocol, cisplatinum was replaced by carboplatinum (400 mg/m²/cycle) (15). The results were less favorable with this regimen than with the British JEB regimen. This difference was mainly attributed to the lower single and cumulative dose of carboplatinum. In the recent French protocol, alternating combinations of cisplatinum with etoposide or ifosfamide are administered, resulting in a superior response rate compared to the previous carboplatinum based strategy.
In both the French TGM 90 and the British GC II studies, the analysis of prognostic factors revealed the prognostic impact of high AFP serum levels at diagnosis, this results were not repeated in other study groups who used a cisplatinum based regimen as well as in the ongoing French protocol.

The German protocols for testicular (MAHO) and nontesticular (MAKEI) GCTs included cisplatinum- and etoposide based chemotherapy regimens. As a result of the excellent event-free survival rates above 80% achieved with the first MAKEI and MAHO protocols, the cumulative chemotherapy was step-wise reduced to 4 resp. 5 cycles without effecting outcome (16). In addition, a risk stratification of chemotherapy according to age, site, histology, stage and completeness of resection has been introduced. According to the current MAKEI 96 protocol, an expectant watch-and-wait strategy is recommended for patients with completely resected low stage tumors. However, patients that relapse during the expectant follow-up require a more intensive regimen with four cycles of three-agent chemotherapy, and as a consequence, therapy is intensified in these patients. In locally advanced and/or metastatic tumors a neoadjuvant approach appears beneficial as it facilitates complete tumor resection and thereby reduces the need for second look surgery (7,8).

**SIOP-CNS-GCT 96 protocol on malignant intracranial GCT**

Therapy for malignant intracranial GCT is stratified according to the histologic differentiation (i.e. germinoma vs. secreting GCT) and initial dissemination (16,17). The ongoing SIOP CNS GCT protocol aims to evaluate achieve standard diagnostic procedures which is measurement of markers in serum/CSF, a CSF-cytology and an MRI of head and spine in all patients. Two different therapeutic options in intracranial germinoma with regard to both their therapeutic impact and their specific acute and long-term toxicity. For secreting intracranial tumors and embryonal carcinoma, the effect of a combined treatment with PEI and radiotherapy adapted to dissemination is examined.

In pure intracranial germinoma, which account for 50% of all intracranial GCT and do not secret significant amounts of HCG/ß-HCG, a histologic verification of the tumor is mandatory. According to the current SIOP CNS GCT 96 protocol patients with germinoma and localized disease can be treated either with craniospinal irradiation with 24 Gy and a tumor boost of 16 Gy or with a multimodal treatment including two cycles of chemotherapy (CarboPEI) followed by a focal irradiation (40 Gy). In metastatic disease craniospinal irradiation and boost to tumor and the metastatic sites is the treatment of choice. Data achieved so far concerning effect of chemofocal and focal treatment reveal that this approach bears a higher risk of ventricular relapses (18,19). Therefore additional ventricular treatment is implemented in new protocols for localized CNS germinoma. It has been demonstrated that a 5 year event free survival of 91% and 5 year overall survival of 94% can be achieved by radiotherapy only (20), whereas due to the higher risk of ventricular failures the 5 year event free survival of patients treated with a combined treatment is about 85% and the five year overall survival is 92%. As another important risk factor incomplete staging in germinoma especially focussing on marker evaluation in serum /CSF was detected. More then 50% of the relapsing patients show secretion of markers which had not been measured at initial diagnosis of a germinoma. The secreting intracranial GCT (YST, CHC, EC) show an inferior prognosis compared to germinoma. In these patients 4 cycles of cisplatinum based chemotherapy (PEI, Table 4) are applied, followed by a delayed tumor resection and radiotherapy. The radiotherapy is stratified according to the initial staging. Non-metastatic tumors receive focal irradiation (54 Gy), whereas patients with intracranial or spinal metastases or tumor cells in the CSF receive a craniospinal irradiation (30 Gy plus 24 Gy tumor boost). The summary of several cooperative protocols and the preliminary data of the SIOP CNS GCT 96 protocol suggest that a long term remission can be obtained in about two thirds of patients. In the SIOP CNS GCT 96 protocol as clinical risk factors AFP>1000 ng/ml at diagnosis and residual disease after the end of treatment were defined and will be used for definition of risk groups in the forthcoming SIOP CNS GCT II protocol. Additionally in germinoma and non-germinoma; strategies that utilized chemotherapy and excluded radiotherapy have resulted in only insufficient tumor control (21).
Table 3: Standard chemotherapy regimens in pediatric GCT

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage and Duration</th>
<th>Cycles</th>
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<tr>
<td><strong>PEI</strong></td>
<td>(MAKEI 96, SIOP CNS GCT 96, MAHO 98, SFOP)</td>
<td></td>
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<tr>
<td>Cisplatin$^1$</td>
<td>20 mg/m² over 1 h Day 1,2,3,4,5</td>
<td>2-4</td>
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<tr>
<td>Etoposide</td>
<td>100 mg/m² over 3 h Day 1,2,3</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide$^2$</td>
<td>1500 mg/m² over 20 h Day 1,2,3,4,5</td>
<td></td>
</tr>
<tr>
<td><strong>PVB</strong></td>
<td>(MAHO 98)</td>
<td></td>
</tr>
<tr>
<td>Cisplatin$^1$</td>
<td>20 mg/m² over 1 h day 4,5,6,7,8</td>
<td></td>
</tr>
<tr>
<td>Vinblastin</td>
<td>3 mg/m² or 0.15 mg/kg i.v. bolus day 1,2</td>
<td></td>
</tr>
<tr>
<td>Bleomycin$^3$</td>
<td>15 mg/m² over 24 h day 1,2,3</td>
<td></td>
</tr>
<tr>
<td><strong>BEP</strong></td>
<td>(MAHO 98)</td>
<td></td>
</tr>
<tr>
<td>Bleomycin$^3$</td>
<td>15 mg/m² over 24 h day 1,2,3</td>
<td>3</td>
</tr>
<tr>
<td>Etoposide</td>
<td>80 mg/m² over 3 h day 1,2,3,4,5</td>
<td></td>
</tr>
<tr>
<td>Cisplatin$^1$</td>
<td>20 mg/m² over 1 h day 4,5,6,7,8</td>
<td></td>
</tr>
<tr>
<td><strong>BEP</strong></td>
<td>(US-Childrens Oncology Group)</td>
<td></td>
</tr>
<tr>
<td>Bleomycin</td>
<td>15 mg/m² over 24 h day 1</td>
<td>4</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m² over 3 h day 1,2,3,4,5</td>
<td></td>
</tr>
<tr>
<td>Cisplatin$^1$</td>
<td>20 mg/m² over 1 h day 4,5,6,7,8</td>
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<tr>
<td><strong>High-dose BEP</strong></td>
<td>(US-Childrens Oncology Group)</td>
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<tr>
<td>Bleomycin</td>
<td>15 mg/m² over 24 h day 1</td>
<td>4</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m² over 3 h day 1,2,3,4,5</td>
<td></td>
</tr>
<tr>
<td>Cisplatin$^1$</td>
<td>40 mg/m² over 1 h day 1,2,3,4,5</td>
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<tr>
<td><strong>JEB</strong></td>
<td>(UKCCSG GCII)</td>
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<tr>
<td>Carboplatinum</td>
<td>600 mg/m² over 1 h day 2</td>
<td>5</td>
</tr>
<tr>
<td>Etoposide</td>
<td>120 mg/m² over 1 h day 1,2,3</td>
<td></td>
</tr>
<tr>
<td>Bleomycin$^3$</td>
<td>15 mg/m² over 15 min day 3</td>
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<tr>
<td><strong>CarboPEI</strong></td>
<td>(SIOP CNS GCT 96)</td>
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</tr>
<tr>
<td>Carboplatinum</td>
<td>600 mg/m² over 1 h day 1</td>
<td>2</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m² over 3 h day 1,2,3,22,23,24</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide$^2$</td>
<td>1800 mg/m² over 3 h day 22,23,24,25,26</td>
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$^1$ plus mannitol forced diuresis, $^2$ plus Mesna uroprotection, $^3$ omitted in children < 1 year, 7.5 mg/m² in children < 2 years
Follow-up

A complete clinical remission is defined as normalization of the tumor-markers within the age-related normal range and the absence of suspicious residual structures, even in patients with normalized tumor markers, as these structures may represent remaining mature teratoma. Most relapses occur within the first two years after diagnosis. However, in some patients late recurrences up to five years after diagnosis of malignant ovarian GCT or intracranial germinoma have been observed. Therefore, the initial follow-up examinations after completion of chemotherapy have to be performed in short intervals, (i.e. weekly) controls of the tumor markers AFP and β-HCG early during follow-up. In watch-and-wait patients, the decline of the AFP values is evaluated with regard to its serum half-life of approximately 6 to 7 days.

In addition, the follow-up examinations include repeated imaging of the primary site of tumor. In case of residual structures after chemotherapy of extracranial GCT, resection of these residues is indicated, since mature teratoma may have remained and bear the risk of tumor progression.

In intracranial tumors, endocrinologic tests at diagnosis and during follow-up are mandatory. Also a distinct neurological and if possible neuropsychological evaluation should be obtained. In children treated with cisplatinum-containing polychemotherapy (esp. plus ifosfamide), the renal function has to be monitored carefully for tubular nephropathy and at diagnosis and before every course of platinum based treatment audiometry should be performed.

Relapse treatment

In patients with recurrent or refractory tumors who had previously been treated with a non-platinum or carboplatinum therapy, cisplatinum-based regimens (preferably PEI) have been successfully applied. Therefore, cisplatinum containing regimen in patients with relapsed tumors are prefered, if the organ toxicities related to the previous treatment allow further cisplatinum therapy. Patients suffering from severe cisplatinum-related toxicity may be treated with a combination of carboplatinum and high dose etoposide (at 400-600 mg/m² on 3 days). Otherwise, there is no international consensus on strategies for treatment or recurrent GCTs. More than 90% of relapses occur at the primary site of the tumor. Therefore, relapse chemotherapy has to be accompanied by an intensive local therapy, preferably complete resection of the recurrent tumor after tumor-reduction by preoperative chemotherapy. It could be demonstrated that patients with local recurrences and poor response to conventional chemotherapy may profit from locoregional hyperthermia combined with platinum-based chemotherapy. Lastly, high dose local irradiation at doses above 45 Gy has shown some beneficial effect after incomplete resection of the tumor recurrence (22).

For malignant CNS GCT, especially of non-germinomatous histology which failed after first line treatment the chance to achieve a second remission is small. Reports from the French SFOP series and observation within SIOP CNS GCT 96 are that although tumors respond very well again to chemotherapy only in cases with complete biological, removal of any residual tumor and successful applied high dose treatment with additional irradiation a second remission could be achieved.

Future perspectives

A multimodal approach that utilizes cisplatinum/etoposide chemotherapy as well as tumor resection is highly effective for the treatment of paediatric GCTs. In the light of the high cure rates achieved by current protocols, research must now focus on new aims. Patients should be identified that are only at a low risk of relapse, and in whom adjuvant chemotherapy can either be withheld or significantly reduced, thus allowing to minimize the impact on short- and long-term quality of life, and treatment toxicity. In this context, molecular genetic studies might also reveal some important information that may be utilized for risk stratification. For this rare disease especially for unfavourable sites like CNS tumors international cooperation is vital. Another todays demand is the focus on rehabilitation, reintegration and Quality of Life of the cured patients to determine their quality of survival and if impaired to consider these results for future treatment planning.
References


