Pergamon

European Journal of Cancer Vol. 33, No. 6, pp. 895–902, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00157-3

# Paediatric Update

# Malignant Germ Cell Tumours in Childhood

C.R. Pinkerton

Children's Department, The Royal Marsden NHS Trust and Institute of Cancer Research, Downs Road, Sutton, Surrey SM2 5PT, U.K.

THOUGH RELATIVELY rare, malignant germ cell tumours (MGCT) are one of the few highly curable types of cancer in adults. Dramatic improvements in outcome came in the 1980s with the introduction of cisplatin-based chemotherapy regimens combined with bleomycin and vinblastine (PVB). The subsequent use of etoposide, in place of vinblastine (BEP), reduced early morbidity [1], and the effective 5-$HT_3$ antagonists for cisplatin-induced emesis further improved tolerance. PVB and BEP were first used in MGCT by Pritchard and coworkers in the late 1980s [2] with encouraging results, and a range of similar regimens produced outcomes in advanced and metastatic disease not achievable with earlier VAC (vincristine, doxorubicin, cyclophosphamide) type protocols.

Whilst it is gratifying to see overall survival curves showing excellent results for most MGCT in childhood, particularly those of gonadal origin, there is no room for complacency. There are still subgroups in which over half the children experience relapse and many patients receive curative chemotherapy that is unnecessarily toxic—with a risk of sterilisation, cardiomyopathy and second cancers. Others may receive chemotherapy where it is not required for cure. Much also remains to be learned about the biology of this complex group of tumours and recent molecular genetic studies throw new light on potentially important differences between childhood and adult MGCT. This Update addresses some of these issues within the context of recent experience in the U.K. and other published paediatric studies. Only extra-cranial MGCT will be considered, as intracranial MGCT will be covered in a subsequent Update.

## TUMOUR ORIGIN AND PATHOLOGY

MGCT develop at points along the normal migration pathway of germ cells during embryogenesis. Arising in the yolk sac endoderm, cells migrate along the paravertebral gonadal ridge in a caudal to cranial direction. Apart from the gonads, MGCTs usually arise in the midline structures—the midbrain, mediastinum, retroperitoneum and sacrococcygeal region. The morphological subtype reflects the differentiation pathway to which the cell becomes committed as a consequence of both molecular genetic changes and local environmental factors (Figure 1).

There are clear differences between MGCTs in children and in adults, both in composition and distribution [3, 4]. In prepubertal children, tumours at extragonadal sites are commoner in children and most MGCT contain yolk sac elements. Most testicular tumours in young children are 'pure' yolk sac tumours ('orchioblastomas'). Embryonal carcinomas are rare and seminomas are hardly ever seen. Pure germinomas are almost exclusively found in the ovary (dysgerminomas) or central nervous system. Sarcomatous components are less common in childhood, although rhabdomyosarcoma and angiosarcoma may be found particularly in mediastinal tumours [5].

## MOLECULAR PATHOLOGY

DNA ploidy and cytogenetics have been most extensively studied in adult testicular tumours. Aneuploidy and the presence of isochromosome 12p (i12p), i.e. two copies of the short arm of chromosome 12, are common features [6]. It has been suggested that i12p may be detected in virtually all testicular tumours if molecular methods such as fluorescent *in situ* hybridisation (FISH) are used [7]. This cytogenetic abnormality seems to occur irrespective of the pathological subtype, indicating a possible role early in pathogenesis. i12p has also been described in some mediastinal, ovarian and pineal tumours [8].

i12p is generally found only in adolescent testicular or mediastinal disease [9–11]. Haematological malignancies, usually acute non-lymphoblastic leukaemia, associated with germ cell tumours may also exhibit i12p, suggesting that the leukaemia has arisen from the teratomatous tumour rather than a bone marrow stem cell [12]. The gene for mast cell growth factor (MGF; Steel factor) is located at 12q22 which is also involved in testicular development.

i12p is not found in orchioblastomas in children under 5 years old, unlike in adults. These tumours are generally diploid or tetraploid [13]. Loss of parts of chromosome 1 (particularly deletion of 1p36), 3 and 6 have been detected by conventional karyotyping and FISH [14].

## INCIDENCE AND EPIDEMIOLOGY

Germ cell tumours account for approximately 3% of all childhood malignancies and data from the U.K. National

Received 13 Mar. 1997; accepted 20 Mar. 1997.

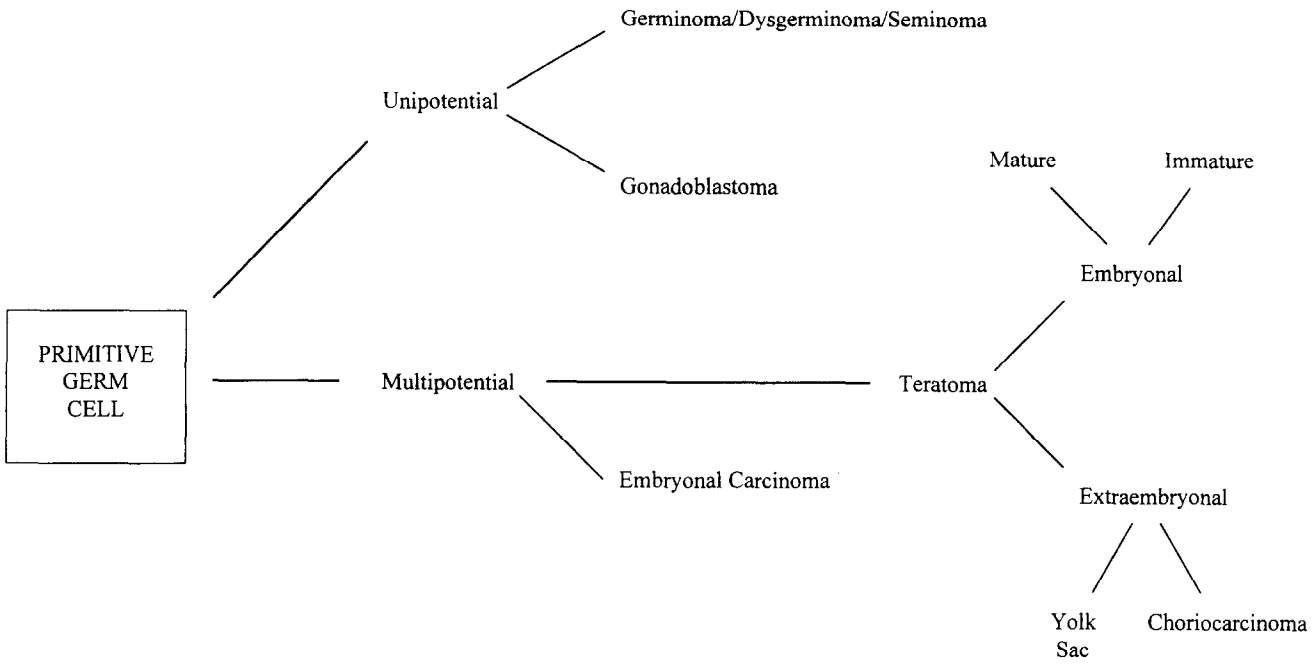


**Figure 1. Scheme of differentiation pathway for MGCT.**

Registry of Childhood Cancer in Oxford shows an annual incidence of 1.5 per million children under 15 years for gonadal germ cell tumour and 0.9 per million for non-gonadal germ cell tumours. The overall sex ratio is approximately equal. The relative incidence according to age, site and pathological subtype are listed in Table 1. There is a bimodal age distribution, with one peak in children under 3 years of age, reflecting the incidence of sacrococcygeal tumours. The second peak occurs after the age of 12, due to malignant germ cell tumours of testis and ovary.

An increased incidence of germ cell tumours, usually benign gonadoblastoma, is reported in children with dysgenic gonads. Congenital abnormalities associated with germ cell tumours include defects in the urogenital tract, such as cryptorchidism, anorectal anomalies and sacral agenesis. Tumours associated with cryptorchidism tend to be malignant. Both benign and malignant germ cell tumours are found in children with the Klinefelter's syndrome, frequently in the mediastinum or central nervous system.

## STAGING SYSTEMS

In the past, these have been derived from adult classifications and have been site oriented with multiple subgroups. With the advent of highly effective chemotherapy these are now inappropriate. The aim of any staging system should be to distinguish patient groups on the basis of outcome and this is clearly not the case with the older systems. For example, the FIGO staging system for ovarian tumours, with no less than 10 subgroups, is unnecessarily complex, as are adaptations of both ovarian and testicular tumour staging systems. Table 2 outlines a suggested staging system which will be suitable for extra-cranial MGCT irrespective of site. An alternative grouping proposal from North America comprises three categories:

- 'low risk'—immature teratoma and completely resected gonadal or sacrococcygeal MGCT;
- 'intermediate risk'—unresectable gonadal and extragonadal tumours and metastatic gonadal (this group includes patients from the low risk group who were treated with surgery alone and developed local recurrences); and

*Table 1. Relative incidence according to age and pathology*

| Site | Relative incidence (%) | Age | Pathology |
|---|---|---|---|
| Sacrococcyx | 35 | Neonate | Teratoma: mature 65%, immature 5%, malignant 10–30% |
| Ovary | 25 | Early teens | Teratoma: mature 65%, immature 5%, malignant 30% (Pure yolk sac 30%, mixed 30%) |
| Testis | 20 | Infant and adolescent | Teratoma: mature 20%, malignant 80% (Yolk sac 90%, germinoma 10%, embryonal carcinoma 1–5%) |
| Cranium | 5 | Child | Germinoma 20–50% Embryonal carcinoma 20–50% Mature teratomas 20–30% |
| Mediastinum | 5 | Adolescent | Teratoma: mature 60%, mixed 20% Embryonal carcinoma 20% |
| Retroperitoneum | 5 | Infant | Teratoma: mature or immature, rarely malignant |
| Head and neck | 3 | Infant and neonate | Usually mature teratoma, immature rarely malignant |
| Vagina | 2 | Infant | Usually yolk sac |

*Table 2. Staging system for malignant germ cell tumours in childhood for all extracranial sites, i.e. ovary, testis and other extragonadal sites*

| | |
|---|---|
| Stage 1 | Complete resection of primary tumour with subsequent fall of markers |
| | No nodal involvement on CT or at surgery |
| Stage II | Microscopic residual disease at surgical margins |
| | Transcrotal resection or biopsy |
| Stage III | Gross residual disease or biopsy only |
| | ±nodes positive on imaging |
| | Contiguous visceral involvement in the case of ovary, i.e. omentum, intestine, bladder |
| | Diffuse tumour spill at surgery |
| Stage IV | Distant metastases to liver, lung, bone, bone marrow, distant nodes, brain |

- 'high risk'—unresectable or metastatic extragonadal tumours and patients recurring with extensive primary or metastatic disease after initial treatment with surgery alone.

Patients with surgically completely resected tumours, no measurable secondary tumours and rapidly declining α-fetoprotein (AFP) and β-human chorionic gonadotropin (beta-HCG) levels can be observed without receiving chemotherapy, and most do well. Metastatic disease at any site requires intensive chemotherapy. It remains to be shown to what extent other stages can be distinguished and this requires retrospective analysis of clinical data using the above systems. The ability to distinguish good and intermediate risk non-metastatic disease is essential for future studies that will address reduction in chemotherapy intensity. Conversely, if poor risk groups can be clearly identified more aggressive multi-agent regimens can be evaluated.

Who are likely to be the high risk patients? Studies in adults with disseminated disease have revealed a number of adverse prognostic features, including the level of serum markers (AFP and β-HCG), bulky disease and sites and numbers of metastases [15, 16], but these factors have not been adequately evaluated in children. The initial level of a tumour marker is probably of less importance than the rate of decline and eventual normalisation. A slow decline may reflect relative chemoresistance at an early stage and persistent elevation is usually due to persistent active tumour, which must be eliminated by surgery, second-line/dose intensive chemotherapy or irradiation. The poorer outcome is at sites where complete surgical clearance is likely to be more difficult, i.e. extra-gonadal and CNS sites. As with many solid and haematological malignancies, tumour bulk may be an adverse factor, e.g. massive mediastinal or sacrococcygeal tumours with extensive intra-abdominal extension. Bone or marrow are rare sites for metastasis in children but probably also have adverse prognostic significance.

## INDIVIDUAL TUMOUR SITES

*Sacrococcygeal tumours*

This site accounts for 35–40% of tumours, and half occur in neonates, mainly girls. Tumours may be so large that delivery of the baby is difficult. Although most are benign tumours, the likelihood of malignancy correlates with the initial extent of tumour. Approximately one third of those with extensive intra-abdominal or intraspinal extension will contain malignant component, almost invariably yolk sac tumour.

Predominantly extra-abdominal tumours will have few additional clinical signs in contrast to a pre-sacral lesion which may present urinary frequency, lower extremity weakness and constipation. Ultrasound examination is of benefit in demonstrating abdominal disease but CT or MRI are essential to define clearly the intra-abdominal extent prior to any attempt at surgical excision.

Most of these tumours are initially treated by surgical excision. It is essential that the entire coccyx is removed, otherwise the local recurrence rate is high. If the tumour is unresectable due to regional extension, then multiple biopsies should be performed, as these may reveal a malignant component which would justify primary chemotherapy. In the absence of histological evidence of malignancy, empirical use of chemotherapy in these small infants is unjustified, as morbidity may be high. The use of serum AFP as a tumour marker is difficult in this age group, particularly during the first month when normal levels may be in the thousands, because the level does not fall into the normal adult range until the infant is at least 6 months of age. After surgery, AFP levels should be monitored to document a normal decline and should be repeated for up to 2 years after surgery, as disease recurrence may occur during this period. Initially, benign tumours may relapse as MGCT, usually of yolk sac subtype. Recurrence may be detected preclinically by serial AFP measurements.

*Mediastinal tumours*

These tumours occur in the anterior mediastinum and are more common in adolescent males [17]. They usually present with tracheal or bronchial compression. Occasionally, ectopic production of insulin or sex hormones may result in hypoglycaemia or precocious puberty. In adolescent females these tumours are generally benign; however, there may be a malignant component. Where there is evidence of malignancy from elevated tumour markers, i.e. AFP, β-HCG or from a tumour biopsy, attempts at surgical resection are not appropriate and may result in unnecessary morbidity, such as phrenic nerve palsy. Primary chemotherapy is indicated, followed by surgical removal of any residual tumour.

*Ovarian tumours*

Approximately 30% of GCT arise in the ovary and up to 5% of cases are bilateral. The peak incidence is around 10 years of age and 70% are benign mature cystic teratomas. The tumour is often asymptomatic until it reaches a large size, or may present with torsion, infarction or rupture. Approximately one third of ovarian GCT will contain malignant components and detailed histological examination of any solid element in the teratoma is mandatory [18]. With

malignant disease the pattern of spread is usually that of peritoneal implants with ascites and distant metastases to lymph nodes, liver and lung. It should be emphasised that 'gliomatosis peritonei', i.e. presence of mature neuroglial tissue within the peritoneum in association with a mature teratoma, does not adversely influence prognosis or require systemic chemotherapy.

Staging investigations in the case of advanced malignant tumours should include CT scan of chest and abdomen, bone scan and bone marrow assessment. With localised tumour, complete surgical excision is curative, irrespective of the nature or extent of malignant component within the tumour. Tumour markers if elevated at presentation should be closely followed as failure of the AFP to fall within a half-life of approximately 7 days, or β-HCG within a half-life of 24 h, indicates persisting active tumour, which will necessitate chemotherapy. If there is no tumour marker, close surveillance with CT or ultrasound is required. With incompletely resected or unresectable tumours primary chemotherapy is indicated and is usually highly effective. As modern regimens should not be sterilising, bilateral oophorectomy is to be avoided in the case of bilateral disease. Following maximum response to chemotherapy, excision of the primary tumour and localised excision of the contralateral lesion mean that fertility and hormonal function can often be preserved. In an era of effective chemotherapy, extensive mutilating surgery as a primary procedure is never justified.

The management of immature teratoma in the ovary is somewhat controversial. These tumours comprise around 10% of ovarian neoplasms and usually affect children in their early teens. Immature teratoma *per se* in childhood should probably not be regarded as malignant, as its natural history is almost invariably benign. The situation has become somewhat confused because of the inclusion of patients with mixed tumours, as indicated by raised AFP levels. The mainstay of treatment for these tumours should therefore be surgical and one could argue for a 'wait and watch' policy following incomplete resection, rather than elective aggressive use of chemotherapy as for true malignant germ cell tumour.

*Testicular tumours*

This group represents approximately 10% of paediatric GCT. Most patients are less than 4 years old. One risk factor for development during childhood is the presence of an undescended testicle. Around 10% of adults with testicular cancers are found to have had an undescended testicle and the theoretical risk of testicular cancer has been estimated to be up to 50-fold higher in those with cryptorchid testes. To what extent orchidopexy reduces the risk of tumour developing is unclear but should at least facilitate an early diagnosis. For this reason surgery is advised on the undescended testicle somewhere between 6–18 months of age. In children, 80% of testicular tumours will be malignant and the remainder mature benign teratomas [19, 20].

Lymph node and lung metastases are commonest, whilst bone and bone marrow spread is unusual. There is no longer any indication for retroperitoneal lymphadenectomy as part of the staging and defined CT scanning and MRI techniques should detect significant nodal involvement. Moreover, most patients with positive lymph nodes would have elevated tumour markers (AFP or β-HCG) after surgery. In the few patients who appear to have had complete removal of all tumour at presentation but subsequently relapse, usually in abdominal nodes or the lung, the salvage rate is very high and most patients will be cured following chemotherapy and sometimes second surgery. For these reasons, the potential unwanted sequelae of lymphadenectomy, especially impotence and retrograde ejaculation, cannot be justified.

Resection of testicular tumours should be via the high inguinal route ('radical orchiectomy') in order to ensure adequate excision of the cord and avoid skin contamination. Trans-scrotal biopsies are absolutely contra-indicated. In any child with a suspicious testicular mass, urgent serum AFP measurement is mandatory.

*Other sites*

Abdominal germ cell tumours may occur in the retroperitoneal region, stomach, liver and almost any other organ. Hepatic teratoma may present a difficult differential diagnosis from hepatoblastoma, because in both cases serum AFP levels are usually very high. Tumours presenting in the vagina appear as a polypoid friable mass, often superficially resembling botryoid rhabdomyosarcoma, and are generally of pure yolk sac histology. Tumours also arise in the head and neck, with primaries in the nasopharynx, oral cavity, orbit or cervical region. These tumours are usually benign and treated with surgery alone.

## ROLE OF SURGERY IN MGCT

Non-mutilating surgery is indicated at presentation because even in this chemosensitive tumour there is a risk of resistant clones developing or being selected out by a range of molecular mechanisms. Initial complete resection is, however, generally limited to gonadal sites. Operability can be reasonably accurately predicted by CT/MRI and futile attempts at debulking may lead to more harm than good. In other cases a diagnostic biopsy is all that is required. In exceptional circumstances where this procedure may be hazardous, e.g. massive mediastinal tumour with respiratory embarrassment, it may be more appropriate to treat with primary chemotherapy on the basis of raised AFP or β-HCG alone.

With effective chemotherapy there is no longer any place for retroperitoneal nodal resection as a staging procedure or as part of primary therapy of any subtype. Complete excision of any residual mass after chemotherapy is important to guarantee local control. When excision is incomplete, decisions regarding local irradiation will depend upon the histological features of the resected tumour. Where this is entirely differentiated and serum markers are normal, a conservative policy may be applied, particularly in the small child [21, 22].

## IRRADIATION

Radiation now has little role in the management of germ cell tumours in children. Although it is still in use for pure germinomas in adults, e.g. testicular seminoma with nodal involvement, this is not appropriate in children, in whom this highly chemosensitive tumour should be managed as for any other malignant histological subtype. Although extended field radiotherapy may be curative, the likely late sequelae make this unacceptable practice in children. However, radiotherapy may be unavoidable where there is residual

measurable tumour after second-line chemotherapy and surgery for relapsed disease.

## CHEMOTHERAPY

Localised gonadal tumours were curable with the standard VAC regimen and with the escalation of the doses in this protocol, more advanced tumours could also be cured [23]. Although in children there has been no randomised comparison between high dose VAC (vincristine, actinomycin-D, cyclophosphamide) and cisplatin/carboplatin-based regimens, such as PVB or BEP, historical comparison suggests that outcome is superior with hybrid regimens [4]. It is likely that the more recent VAC type protocols with high dose cyclophosphamide (approximately 2 g/m$^2$) or ifosfamide (6–9 g/m$^2$) would be adequate for many tumours. However, the late sequelae of these agents, i.e. infertility in males and cardiac toxicity, are unacceptable when very high cure rates can be achieved with platinum-based chemotherapy.

Undoubtedly, there are some late toxicities with both PVB and BEP, although with limited total dose these sequelae should not be severe [24, 25]. Decline in glomerular filtration rate and high tone hearing loss on audiometry is almost inevitable where the cumulative dose of cisplatin exceeds 3–400 mg/m$^2$ (as is given to most patients). Although not routinely used in MGCT regimens, continuous infusion of cisplatin over 24–48 h is likely to reduce both these toxicities. Peripheral neuropathy is unusual in children, even with very high dose regimens. Pulmonary toxicity is unacceptably high where weekly bleomycin is used, and a number of deaths due to pneumopathy occurred in earlier UKCCSG studies. Persistent skin pigmentation and Raynaud's phenomenon are also regarded as attributable to bleomycin. Fertility may be adversely affected, but some cured female patients have conceived, although there are few data on the fertility of survivors of childhood malignancies [26].

Although a theoretical problem, there is little evidence that second cancers occur due to three-weekly etoposide where cumulative dose is low. Moreover, secondary AML may be biologically associated with MGCT irrespective of the treatment regimen used [27–29]. Vinblastine is less well tolerated than etoposide and no more effective. The BEP regimen therefore remains the gold standard chemotherapy for paediatric MGCT, with excellent outcome and moderate sequelae.

## CAN CARBOPLATIN BE USED IN PLACE OF CISPLATIN?

It is becoming clear from randomised studies in adult MGCT that cisplatin is superior to carboplatin when both drugs are used at standard dose levels. In patients with good risk testicular tumours, etoposide and carboplatin (EC) appeared inferior to etoposide and cisplatin (EP). Although no difference in response rates were seen between EC (88%) and EP (90%) the relapse rates were 12% and 3%, respectively [30]. This confirms an earlier, similar study in which a higher dose of carboplatin (350 mg/m$^2$) was given, where the difference in failure rate was 30% versus 9% [31]. Unfortunately, these trials included a range of carboplatin doses from 350–500 mg/m$^2$ and no attempt was made to dose on the basis of renal function. However, in the MRC trial comparing carboplatin/etoposide/bleomycin (CEB) with cisplatin/etoposide/bleomycin (BEP) for four cycles, there was again a significantly higher failure rate in patients on CEB (19% versus 10%) [32]. In this trial an AUC of 5 was applied. In a more recent randomised study in good risk metastatic non-seminomatous MGCT, again using an AUC of 5 and full dose weekly bleomycin for four cycles, there was no difference in initial response rates (76% for CEB and 81% for PEB) but more patients relapsed following the carboplatin based protocol (32% versus 13%) [33]. Comparative studies have not been performed in children. A small study by the French SFOP group evaluated carboplatin 400 mg/m$^2$ with cisplatin 100 mg/m$^2$ combined with cyclophosphamide, actinomycin, vinblastine and bleomycin in 42 children with non-metastatic GCT. The CR rate was significantly lower for the carboplatin based protocol; 60% versus 89% [34]. A reservation about this trial was the low dose of carboplatin (400 mg/m$^2$) and the failure to apply a GFR-based dose schedule.

Results in the U.K. have been in marked contrast. Several years ago a pilot protocol, using the JEB regimen (carboplatin, etoposide, bleomycin) was reported. Although the numbers were small, the outcome including those with advanced disease was encouraging [35]. This regimen formed the basis of the current UKCCSG GC2 trial in which the carboplatin dose was based on the Royal Marsden protocol [36], using the Calvert/Newell formula (dose mg) = desired AUC × uncorrected GFR + 20. An AUC of 6 was used. An AUC of 4 has been suggested as the minimum effective value in adults and the higher AUC of 6 is well tolerated in children. Preliminary results for non-gonadal tumours, reported at the 1996 SIOP meeting, showed an overall event-free survival of 64% using JEB in GC2 compared with 56% in an historical group of patients treated with BEP [37]. The absence of renal and hearing impairment in the JEB protocol were confirmed. Current unpublished data regarding gonadal tumours show an event-free survival of over 90% and it seems likely that, provided that the higher dose of carboplatin based on GFR is used, cisplatin-related toxicity can be avoided in children without compromising efficacy [38]. To what extent this assumption can be made in future studies where bleomycin is omitted, or only high risk patients are considered, remains to be seen.

## CAN BLEOMYCIN BE OMITTED?

In the original PVB (BEP) regimes in adults, bleomycin was given weekly as a 30 min infusion, but current UKCCSG policy is to administer bleomycin once very 3 weeks, as a continuous 24 h infusion. This strategy of modified dose and schedule appears to have reduced lung toxicity, although the long-term significance of subclinical lung function abnormalities still has to be clarified. A number of randomised studies in adults have addressed the issue of the importance of bleomycin in combination chemotherapy and the overall conclusion has been that bleomycin does have a significant role to play. In a comparison of PB versus PVB, the CR rate was comparable (89% versus 94%), but the eventual death rate from progressive malignancy was 15% in the PV group versus 5% in PVB. The overall survival difference was not significant, due to a higher proportion of toxic deaths with the three drug regimen due to both septicaemia and lung toxicity [39]. A subsequent study compared BEP with EP in patients with favourable prognosis

disseminated GCT in adults [40]. Again the initial CR rate was comparable but there were a greater number of treatment failures, including persistent active disease in post-chemotherapy resected disease and relapses, resulting in failure-free survival of 86% versus 69% and overall survival of 95% versus 86%. These studies are consistent with data from a number of earlier trials [41–44]. In a small study from Boston, a regimen combining vincristine, cisplatinum and etoposide alternating with standard dose VAC has been described. Only four patients had measurable disease, of whom one required local radiotherapy to achieve CR. All 11 patients have, however, remained disease-free [45].

There is clearly a need to carry out a large multicentre study of a platinum-based regimen to assess the role of bleomycin. This should probably be restricted to standard and favourable risk patients if a consensus can be reached on risk group definition.

## WHAT IS APPROPRIATE SALVAGE THERAPY?

Several active drugs can be used in the event of relapse following the JEB, PVB or BEP regimens. Ifosfamide has been shown to be effective [46] and doxorubicin, actinomycin and methotrexate are also used [47]. Increased dose intensity with previously used drugs may produce responses [48, 49]. The role of very high dose combination chemotherapy, requiring autologous marrow or stem cell rescue, is still uncertain [50, 51], even in adults, and should not be used, except in the research setting.

In children, second-line chemotherapy with a regimen such as IVAd (ifosfamide, vincristine and doxorubicin) may be curative, provided surgically proven CR is achieved. Local irradiation is indicated if the latter is in doubt. High dose therapy should be restricted to refractory tumours or early off-therapy relapses or third CR. There may also be an additional role in very young children where irradiation is to be avoided.

In conclusion, there are still several important issues to be addressed. The most effective, least toxic chemotherapy must be defined in relation to meaningful risk classifications, both in the short- and long-term. Such studies would require large national or international collaborative groups. Despite invaluable clues from adult studies, these answers will not be found simply by extrapolating from adult to paediatric practice.


1. Williams SD, Birch R, Einhorn L, *et al.* Treatment of disseminated germ cell tumors with cisplatin, bleomycin and either vinblastine or etoposide. *N Engl J Med* 1987, **316**, 1435–1440.
2. Pinkerton CR, Pritchard J, Spitz L. High complete response rate in children with advanced germ cell tumours using cisplatin-containing combination chemotherapy. *J Clin Oncol* 1986, **4**, 194–199.
3. Hawkins EP, Perlman EJ. Germ cell tumors. In Parnham DM, ed. *Pediatric Neoplasia.* Philadelphia, Lippincott-Raven, 1996, 297–330.
4. Varicnd S. Germ cell tumors. *Current Histopathology. Paediatric Neoplasia.* London, Kluwer Academic Publishers, 1993, 70–80.
5. Corbett R, Carter R, MacVicar D, Horwich A, Pinkerton CR. Embryonal rhabdomyosarcoma arising in a germ cell tumour. Proceedings of the Tumour Board of the Royal Marsden Hospital, Sutton, Surrey. *Med Pediatr Oncol* 1994, **23**, 497–502.
6. Bosl GJ, Dmitrovsky E, Reuter VE, *et al.* Isochromosome of chromosome 12: clinically useful marker for male germ cell tumors. *J Natl Cancer Inst* 1989, **81**, 1874–1878.
7. Rodriquez E, Mathew S, Mukherjee AB, Reuter VE, Bosl GJ, Chaganti RS. Analysis of chromosome 12 aneuploidy in interphase cells from human male germ cell tumors by fluorescence in situ hybridization. *Genes Chromosomes Cancer* 1992, **5**, 21–29.
8. Atkin NB, Baker MC. Abnormal chromosomes including small metacentrics in 14 ovarian cancers. *Cancer Genet Cytogenet* 1987, **26**, 355–361.
9. Hoffner L, Deka R, Chakravarti A, Surti U. Cytogenetics and origins of pediatric germ cell tumors. *Cancer Genet Cytogenet* 1994, **74**, 54–58.
10. Jenderny J, Koster E, Borchers O, *et al.* Interphase cytogenetics on paraffin sections of paediatric extragonadal yolk sac tumours. *Virchows Archiv* 1996, **428**, 53–57.
11. Perlman EJ, Cushing B, Hawkins E, Griffin CA. Cytogenetic analysis of childhood endodermal sinus tumours: a Pediatric Oncology Group study. *Pediatr Pathol* 1994, **14**, 695–708.
12. Ladanyi M, Samaniego F, Reuter VE, *et al.* Cytogenetic and immunohistochemical evidence for the germ cell origin of a subset of acute leukemias associated with mediastinal germ cell tumors. *J Natl Cancer Inst* 1990, **82**, 221.
13. Silver SA, Wiley JM, Perlman EJ. DNA ploidy analysis of pediatric germ cell tumors. *Mod Pathol* 1994, **7**, 951–956.
14. Perlman EJ, Valentine MB, Griffin CA, Look AT. Deletion of lp36 in childhood endodermal sinus tumors by two-color fluorescence in situ hybridization: a Pediatric Oncology Group study. *Genes Chromosomes Cancer* 1996, **16**, 15–20.
15. Mead GM, Stenning SP, Parkinson MC, *et al.* The second Medical Research Council study of prognostic factors in nonseminomatous germ cell tumors. *J Clin Oncol* 1992, **10**, 85–94.
16. Gerl A, Clemm C, Schmeller N, Hartenstein R, Lamerz R, Wilmanns W. Advances in the management of metastatic nonseminomatous germ cell tumours during the cisplatin era: a single-institution experience. *Br J Cancer* 1996, **74**, 1280–1285.
17. Truong LD, Harris L, Mattioli C, *et al.* Endodermal sinus tumor of the mediastinum. *Cancer* 1986, **58**, 730–739.
18. Orr PS, Gibson A, Young OG. Ovarian tumors in children: a 27 year review. *Br J Surg* 1986, **132**, 587–589.
19. Huddart SN, Mann JR, Gornall P, *et al.* The UK Children's Cancer Study Group: testicular malignant germ cell tumours 1979–1988. *J Pediatr Surg* 1990, **25**, 406–410.
20. Visfeldt J, Jorgensen N, Muller J, Moller H, Skakkebaek NE. Testicular germ cell tumours of childhood in Denmark, 1943–1989: incidence and evaluation of histology using immunohistochemical techniques. *J Pathol* 1994, **174**, 39–47.
21. Toner GC, Panicek DM, Heelan RT, *et al.* Adjunctive surgery after chemotherapy for nonseminomatous germ cell tumors: recommendations for patient selection. *J Clin Oncol* 1990, **8**, 1683–1694.
22. Einhorn LH. Do all germ cell tumor patients with residual masses in multiple sites require postchemotherapy resections? *J Clin Oncol* 1997, **15**, 409.
23. Flamant F, Schwartz L, Delons E, *et al.* Nonseminomatous malignant germ cell tumors in children. Multidrug therapy in stages III and IV. *Cancer* 1984, **54**, 1687–1691.
24. Boyer M, Raghavan D, Harris PJ, *et al.* Lack of late toxicity in patients treated with cisplatin-containing combination chemotherapy for metastatic testicular cancer. *J Clin Oncol* 1990, **8**, 21–26.
25. Bokemeyer C, Berger CC, Kuczyk MA, Schmoll H-J. Evaluation of long-term toxicity after chemotherapy for testicular cancer. *J Clin Oncol* 1996, **14**, 2923–2932.
26. Lampe H, Horwich A, Norman A, Nicholls J, Dearnaley DP. Fertility after chemotherapy for testicular germ cell cancers. *J Clin Oncol* 1997, **15**, 239–245.
27. Pedersen-Bjergaard J, Hansen SW, Larsen SO, Daugaard G, Philip P, Rorth M. Increased risk of myelodysplasia and leukaemia after etoposide, cisplatin and bleomycin for germ-cell tumours. *Lancet* 1991, **338**, 359–363.
28. Vasey PA, Dunlop DJ, Kaye SB. Primary mediastinal germ cell tumour and acute monocytic leukaemia occurring concurrently in a 15-year-old boy. *Ann Oncol* 1994, **5**, 649–652.
29. Nichols CR, Roth BJ, Heerema N, Griep J, Tricot G. Hematologic neoplasia associated with primary mediastinal germ-cell tumors. *N Engl J Med* 1990, **322**, 1425–1429.
30. Bajorin DF, Sarosdy MF, Pfister DG, *et al.* Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in

patients with good-risk germ cell tumors: a multiinstitutional study. *J Clin Oncol* 1993, **11**, 598–606.
31. Tjulandin SA, Garin AM, Mescheryakov AA, *et al.* Cisplatin-etoposide and carboplatin-etoposide induction chemotherapy for good-risk patients with germ cell tumors. *Ann Oncol* 1993, **4**, 633–637.
32. Horwich A, Sleijfer D, Fosså S, *et al.* On behalf of the UK Medical Research Council Testicular Tumour Working Party & EORTC Genito-Urinary Group. A trial of carboplatin-based combination chemotherapy in good prognosis metastatic testicular cancer. *Proc Am Soc Clin Oncol* 1994, **13**, 709 (abstract).
33. Bokemeyer C, Kohrman O, Tischler J, *et al.* A randomized trial of cisplatin, etoposide and bleomycin (PEB) *versus* carboplatin, etoposide and bleomycin (CEB) for patients with 'good risk' metastatic non-seminomatous germ cell tumors. *Ann Oncol* 1996, 7, 1015–1021.
34. Patte C, Baranzelli MC, Quintana E, *et al.* Carboplatin (400 mg/m$^2$) is not as efficient as cisplatinum (100 mg/m$^2$) in childhood non-metastatic non-seminomatous germ cell tumor (NSGCT). Experience of the SFOP. *Med Pediatr Oncol* 1995, SIOP XXVII, 0–47 (abstract).
35. Pinkerton CR, Broadbent V, Horwich A, *et al.* JEB—a carboplatin based regimen for malignant germ cell tumours in children. *Br J Cancer* 1990, **62**, 257–262.
36. Horwich A, Dearnley DP, Nicholls J, *et al.* Effectiveness of carboplatin, etoposide and bleomycin combination chemotherapy in good prognosis metastatic testicular nonseminomatous germ cell tumors. *J Clin Oncol* 1991, **9**, 62–69.
37. Mann JR, Raafat F, Robinson K, *et al.* The UKCCSG's germ cell tumour (GCT) studies: carboplatin, etoposide and bleomycin are as effective as and less toxic than previous regimens for malignant extracranial non-gonadal tumours. *Med Pediatr Oncol* 1996, SIOP XXVIII, 0–41 (abstract).
38. Newell DR, Pearson ADJ, Balmanno K, *et al.* Carboplatin pharmacokinetics in children: the development of a paediatric dosing formula. *J Clin Oncol* 1993, **11**, 2314–2323.
39. Levi JA, Raghavan D, Harvey V, *et al.* The importance of bleomycin in combination chemotherapy for good-prognosis germ cell carcinoma. *J Clin Oncol* 1993, **11**, 1300–1305.
40. Loehrer PJ, Johnson D, Elson P, *et al.* Importance of bleomycin in favorable prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 1995, **13**, 470–476.
41. Germa JR, Sagarra AF, Izquierdo MA, Segui MA. Sequential trials of cisplatin, vinblastine and bleomycin and etoposide and cisplatin in disseminated nonseminomatous germ cell tumors of the testis with a good prognosis at a single institution. *Cancer* 1993, **71**, 796–803.
42. Wozniak AJ, Sampson MK, Shah NT, *et al.* A randomized trial of cisplatin, vinblastine and bleomycin versus vinblastine, cisplatin and etoposide in the treatment of advanced germ cell tumors of the testis: a Southwest Oncology Group Study. *J Clin Oncol* 1991, **9**, 70–76.
43. Bajorin DF, Geller NL, Weisen SF, Bosl GJ. Two-drug therapy in patients with metastatic germ cell tumors. *Cancer* 1991, **67**, 28–32.
44. Brada M, Horwich A, Peckham MJ. Treatment of favourable-prognosis nonseminomatous testicular germ cell tumors with etoposide, cisplatin, and reduced dose of bleomycin. *Cancer Treat Rep* 1987, **71**, 655–656.
45. Frazier AL, Grier HE, Green DM. Treatment of endodermal sinus tumor in children using a regimen that lacks bleomycin. *Med Pediatr Oncol* 1996, **27**, 69–73.
46. Wheeler BM, Loehrer PJ, Williams SD, Einhorn LH. Ifosfamide in refractory male germ cell tumors. *J Clin Oncol* 1986, **4**, 28–34.
47. Levi JA, Thomson D, Harvey V, *et al.* Effective salvage chemotherapy with etoposide, dactinomycin, and methotrexate in refractory germ cell cancer. *J Clin Oncol* 1990, **8**, 27–32.
48. Saxman SB, Nichols CR, Einhorn LH. Salvage chemotherapy in patients with extragonadal nonseminomatous germ cell tumors: the Indiana University experience. *J Clin Oncol* 1994, **12**, 1390–1393.
49. Culine S, Kattan J, Lhomme C, Duvillard P, *et al.* A phase II study of high-dose cisplatin, vinblastine, bleomycin, and etoposide (PVeBV regimen) in malignant nondysgerminomatous germ-cell tumors of the ovary. *Gynecologic Oncol* 1994, **54**, 47–53.
50. Siegert W, Beyer J, Strohscheer I, *et al.* High-dose treatment with carboplatin, etoposide, and ifosfamide followed by autologous stem-cell transplantation in relapsed or refractory germ cell cancer: a phase I/II study. *J Clin Oncol* 1994, **12**, 1223–1231.
51. Rodenhuis S, Westermann A, Holtkamp MJ, *et al.* Feasibility of multiple courses of high-dose cyclophosphamide thiotepa, and carboplatin for breast cancer or germ cell cancer. *J Clin Oncol* 1996, **14**, 1473–1483.

**PII: S0959-8049(97)00171-8**

# Commentary

J. Pritchard

Department of Haematology and Oncology, Great Ormond Street Hospital for Children, NHS Trust, London WC1N 3JH, U.K.

A DIAGNOSIS of Malignant Germ Cell Tumour (MGCT) is one that most paediatric oncologists now receive with a sense of relief at their weekly 'Grand Round', because MGCTs have joined the ranks of the other 'usually curable' childhood solid tumours—Wilms' tumour, Hodgkin's disease, non-Hodgkin's lymphoma, retinoblastoma and hepatoblastoma. This improvement derives from the successful transfer of the 'adult' experience, using cisplatin- or carboplatin-containing regimens in testicular cancer, into paediatric practice. In the early to mid-nineteen eighties, there was considerable resistance to cisplatin-containing therapy because the drug was regarded as 'too toxic' for small children. VAC or VAC-doxorubicin, supplemented by radiation therapy and surgery, were regarded as the 'standard treatment'. Now, however, it is generally agreed that both cisplatin and carboplatin are relatively well tolerated by