CHILDHOOD SOLID TUMOURS OCCURRING IN ADOLESCENTS AND YOUNG ADULTS

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Abstract

A small number of adolescents and young adults are diagnosed with solid tumours that typically occur in childhood – the most common are neuroblastoma, Wilms' tumour and rhabdomyosarcoma. In general, these cancers are often more locally advanced or metastatic when they occur in adolescents and young adults compared with childhood presentations. Multidisciplinary and multimodality care is indicated, usually including surgery, chemotherapy and radiotherapy. Although these tumours often respond to treatment, the overall survival of adolescents and young adults is inferior to that of children. Retrospective analyses of subsets of older patients with Wilms' tumour and rhabdomyosarcoma suggest that prognosis is improved when treatment is delivered according to paediatric guidelines. However, tumour biology must, at least in part, account for the differences in outcome observed between adolescents and young adults and children. A paradigm of cooperative care between adult and paediatric oncologists is encouraged – entry on to age-appropriate clinical trials should be standard of care. Taking these considerations into account, a national Adolescents and Young Adults Cancer Service has been established in New Zealand, premised upon multidisciplinary cooperative care for adolescents and young adults with cancer and their families.

A wide variety of cancers occur in adolescents and young adults (AYA) aged 15-29 years, the most common being lymphoma, skin cancer, thyroid carcinoma and tumours of the testis, ovary and female genital tract.[1] The common extra-cranial solid tumours of childhood account for a small proportion of cancers in AYA. However, these cancers are important. Compared with carcinoma, they are particularly responsive to chemotherapy and radiotherapy; for some tumours, prognosis has been shown to improve when treated according to paediatric trials and guidelines. A paradigm of multidisciplinary care involving close cooperation between adult and paediatric oncologists is essential.[2]

Childhood solid tumours are so-called embryonal tumours – their genesis likely represents an arrest of cellular differentiation with retention of foetal characteristics. However, the biological mechanisms responsible for their occurrence later in life, although currently unclear, are likely to result in more aggressive clinical behaviour.[3] The most common embryonal tumours are neuroblastoma, Wilms' tumour and rhabdomyosarcoma; less common are cancers of the liver (hepatoblastoma) and eye (retinoblastoma).

Neuroblastoma

This tumour is the most common and lethal extra-cranial solid malignancy of childhood, accounting for 8-10% of cancers in patients <15 years of age. Neuroblastoma is the most common cancer of infancy – the median age at diagnosis is 19 months and 98% are detected before 10 years of age.[4] An enigmatic cancer, the biological behaviour spans metastatic tumours that regress spontaneously (stage 4S – table 1) to widely metastatic disease in children older than 18 months that is difficult to cure despite aggressive multimodality therapy. Biological diversity is at least partly explained by genetic changes such as amplification of NMYC oncogene, which confers a dramatically adverse prognosis irrespective of stage.[5]

Table 1: *International Neuroblastoma Staging System[3] (abbreviated)*

Stage 1	Localised tumour with complete gross excision, with or without microscopic residual disease.
Stage 2A	Localised tumour with incomplete gross resection; ipsilateral lymph nodes negative for tumour microscopically.
Stage 2B	Localised tumour with or without complete gross excision, with ipsilateral lymph nodes positive for tumour.
Stage 3	Unresectable unilateral tumour infiltrating across the midline, with or without regional lymph node involvement; or localised unilateral tumour with contralateral lymph node involvement.
Stage 4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organ (except that defined for stage 4S).
Stage 4S	Localised primary tumour (as defined for Stage 1, 2A or 2B) with dissemination limited to skin, liver and/or bone marrow – limited to infants <1 year of age.

Table 2: National Wilms' Tumour Study Group Staging System for Renal Tumours[8]

Stage I	Tumour confined to the kidney and completely resected. No penetration of the renal capsule or involvement of the renal sinus vessels.
Stage II	Tumour extends beyond the kidney but is completely resected (negative margins and lymph nodes). At least one of the following has occurred: (a) penetration of the renal capsule; (b) invasion of the renal sinus vessels; (c) biopsy of the tumour prior to removal.
Stage III	Gross or microscopic tumour remains postoperatively including inoperable tumour; positive surgical margins; spillage of tumour preoperatively or intraoperatively; regional lymph node metastases; or transected tumor thrombus.
Stage IV	Hematogenous metastases or lymph node metastases outside the abdomen (eg. lung, liver, bone, brain).
Stage V	Bilateral renal Wilms' tumour.

The normal tissue counterpart for neuroblastoma is the sympathetic postganglionic nerve cell; most childhood neuroblastoma arises in the abdomen, in particular from the supradrenal medulla, and is characterised by excessive excretion of catecholamine metabolites in the urine. Distant spread is to lymph nodes, bone and bone marrow. Current treatment strategies stratify intensity of therapy according to age at diagnosis, stage (table 1), histological characteristics and genetic aberrations.[4] Low-risk disease is often treated with surgery alone, intermediate-risk with surgery and chemotherapy, and high-risk with induction chemotherapy, surgery, high-dose chemotherapy with haemopoeitic stem cell rescue, radiotherapy and retinoic acid differentiation therapy. Prognosis varies from >95% overall survival for low-risk neuroblastoma to 40% three year event-free survival for high-risk disease.[4]

Less than 3% of neuroblastomas occur in patients older than 10 years of age. Neuroblastoma in AYA differs from that in children in a number of respects:

- Proportionately more advanced (stage 3 and 4) disease at presentation.[6]
- More frequent location of the primary tumour in the chest and pelvis.[7]
- Unusual sites for metastasis – brain, lungs and pleura.[6]
- Elevated urinary catecholamine excretion in only 40% of cases.[7]
- More indolent course characterised by partial response to chemotherapy, followed by multiple and often widespread recurrences. Initial observations led investigators to conclude that neuroblastoma in AYA has a superior outcome (measured by three year event-free survival) compared with children. However, 10-year overall survival declines to around 20%.[6]
- Despite the poor prognosis, few cases are associated with adverse genetic changes characteristic of high-risk childhood neuroblastoma such as NMYC amplification.[8]

The optimal treatment strategy for neuroblastoma in AYA has not been elucidated. However, given the above information, it is logical to conclude that current stratification schema applying to children are less relevant in AYA, particularly those with low-stage disease. Development of and entry on to age appropriate clinical trials is encouraged. Patients up to 30 years of age with high risk neuroblastoma are currently eligible for treatment on the Children's Oncology Group high risk neuroblastoma trial, which compares the efficacy of a single high-dose chemotherapy course (carboplatin, etoposide and melphalan – CEM) with tandem courses (CEM followed by high-dose thiotepa and cyclophosphamide) after intensive induction chemotherapy.*

Wilms' tumour

Typically, this primary renal cancer has a triphasic appearance under the microscope, incorporating blastema, stroma and epithelium, re-enacting the embryonic development of renal tissue from primitive blastemal cells.[9] Wilms' tumour accounts for 6% of childhood cancers; the median age at diagnosis is three to four years. Occasionally, predisposing syndromes are evident, such as hemihypertrophy, aniridia or Beckwith-Wiedemann syndrome. Rarely, the disease is bilateral. Children present with an asymptomatic abdominal mass, haematuria and/or fever. At the time of diagnosis, the tumour has usually destroyed the kidney. With progression, the renal capsule is breached and the tumour spreads to regional lymph nodes, within the renal vein into the inferior vena cava and to the liver and lungs.[9] Treatment is stratified according to stage (table 2) and histology – anaplasia (presence of markedly enlarged polypoid nuclei) confers worse outcome compared with favourable histology Wilms' tumour. Anaplasia is present in 2% of tumours diagnosed in the first two years of life, increasing to 13% in those older than five years.[10]

The therapeutic approach in North America involves primary nephrectomy, histological confirmation and staging. Vincristine and actinomycin D are administered for stages I and II with doxorubicin and radiotherapy added for stages III and IV. In Europe, patients receive pre-operative chemotherapy based on radiological evidence, usually without initial histological confirmation – after six weeks of chemotherapy, nephrectomy is performed with post-operative treatment stratified by staging and histology. Despite this discrepant approach, prognosis is similar with four year overall survival in excess of 90% for stages I-III, and 80% for stage IV.[9]

**Details at www.childrensoncologygroup.org (password-protected)*

Only 1-3% of Wilms' tumours occur in patients >15 years of age. In contrast with children, AYA with Wilms' tumour usually present with flank or abdominal pain and systemic symptoms such as weight loss, anorexia and reduced performance status. Patients do not have bilateral disease or underlying predisposition syndromes. Although the pattern of metastasis is similar to children, AYA present with more advanced disease – 10 of 30 AYA and older adults had evidence of spread to lungs, liver and/or mediastinum.[11] Local histological analysis may be inaccurate; initial diagnoses of renal cell carcinoma and primitive neuroectodermal tumour were altered to Wilms' tumour on subsequent central review of pathology. Occasionally, renal cell carcinoma may coexist with Wilms' tumour. Results reported by Reinhard et al and Kalapurakal et al indicate that the outlook for AYA with non-metastatic Wilms' tumour is similar to that of children.[11,12] This is disputed by Izawa et al who described an inferior outcome despite treatment according to contemporaneous National Wilms' Tumour Study Group trials.[13] Inferior results may, in part, represent lack of familiarity with Wilms' tumour among medical oncologists – in one study, the average interval from surgery to initiation of chemotherapy was 4.7 weeks. Greater chemotherapy-related toxicity is encountered – 13 of 30 patients (43%) suffered grade 3 or 4 vincristine-induced neurotoxicity.[11]

Given the above data, the following is recommended for AYA with Wilms' tumour:

- Central histology review.
- Initial nephrectomy if feasible, percutaneous needle biopsy if not. Oncologists should be dissuaded from the European approach described above, as the clinical presentation and radiology of Wilms' tumour in AYA is indistinguishable from renal cell carcinoma.
- Treatment in close collaboration with a paediatric oncology service and entry on to current Wilms' tumour trials conducted by the Children's Oncology Group or International Society of Paediatric Oncology (SIOP) – maximum age limits for these trials are 30 and 18 years respectively.†

Rhabdomyosarcoma

This tumour, the most common soft tissue sarcoma in children, arises from primitive mesenchymal cells destined towards skeletal muscle differentiation. Rhabdomyosarcoma (RMS) in childhood occurs most commonly in the head and neck and uro-genital regions.[14]

There are two distinct histological variants – embryonal and alveolar; the latter displays greater aggression and is characterised by translocations involving PAX and FKHR genes. Embryonal RMS is the dominant subtype in children. In the AYA population:

- Although the absolute number of STS increases, this entity reduces as a proportion of the total number of cancers – 7.7% of all cancers in 15 to 19 year-olds, the fifth most common diagnosis.
- RMS reduces as a proportion of STS with increasing numbers of synovial sarcoma, malignant peripheral nerve sheath tumour and primitive neuroectodermal tumours (and Kaposi's sarcoma in countries where AIDS is prevalent).
- For those with RMS, there is increasing risk of the alveolar variant.[15]

In contrast with embryonal RMS, alveolar RMS occurs most commonly in the trunk and extremities. Risk stratification for childhood RMS takes into account embryonal v alveolar histology, nodal and metastatic spread, site and size, degree of initial surgical resection and age – those older than 10 years have a worse prognosis.[15] AYA with RMS have large, invasive tumours with greater propensity for metastasis.[16] Taking these variables into account, RMS in AYA is undoubtedly more aggressive compared with that in children.

Approximately 70% of children with RMS are cured employing combinations of surgery, chemotherapy and radiotherapy. The outlook is poorer for AYA and adults with RMS – one study reports five year overall survival of 40%. However, if treatment adheres to paediatric therapy guidelines, overall survival increases to 61%.[17] AYA with RMS should receive treatment according to paediatric strategies; current Children's Oncology Group RMS trials include patients up to 50 years of age, and entry on to such trials for this patient group is encouraged.‡[3]

Hepatoblastoma

Malignancies arising in the liver account for only 1.1% of childhood cancers – 80% of childhood liver cancer is hepatoblastoma. The median age at diagnosis is 16 months; 91% of primary liver cancer in children <5 years old is hepatoblastoma, whereas hepatocellular carcinoma (HCC) accounts for 87% of diagnoses in 15 to 19 year-olds. The child with hepatoblastoma usually presents with an asymptomatic abdominal mass. Occasionally, abdominal pain, anorexia, weight loss and vomiting are encountered. Alfafoetoprotein (AFP) levels are raised in >90% of children. Diagnosis is established after tumour resection if feasible, or following percutaneous core biopsy. Spread is most commonly to the lungs and regional lymph nodes.[18] Prognosis is dependent upon the extent of hepatic involvement, extrahepatic extension and completeness of surgical resection. Childhood hepatoblastoma is chemosensitive – platinum analogues, doxorubicin and 5-fluorouracil are used. The outlook for completely resected non-metastaic hepatoblastoma is excellent.

Few cases of hepatoblastoma have been described in AYA and older adults. Systemic symptoms are more commonly noted in older patients who may present with more advanced disease compared with their infant counterparts.[19] The clinical and radiological features are indistinguishable from HCC. A report of 25 cases of hepatoblastoma in adults noted the following – single large tumour usually located in the right lobe associated with cystic changes, calcification and hypervascularity.

† *Children's Oncology Group trials www.childrensoncologygroup.org (password-protected). SIOP trial www.ukccsg.org (United Kingdom Children's Cancer and Leukaemia Group – password-protected)*

‡ *Children's Oncology Group trials www.childrensoncologygroup.org (password-protected)*

□ *SIOPEL trials www.siopel.org (password-protected)*

Reports suggest that hepatoblastoma in older patients is less responsive to chemotherapy.[20] Complete surgical resection is recommended followed by adjuvant "high-risk" chemotherapy (platinum analogues and doxorubicin); for those with initially unresectable disease, a trial of neoadjuvant chemotherapy is indicated. Given the rarity of this tumour in AYA, treatment according to the International Childhood Liver Tumour Strategy Group (SIOPEL) is recommended.□

Retinoblastoma

Although the most common intra-ocular malignancy of childhood, retinoblastoma is relatively rare with approximately 11 new cases per million children <5 years old. The tumour arises from the embryonic neural retina.[21] Retinoblastoma is unique in that 40% of cases are hereditary, with an underlying germline mutation or deletion in the RB1 gene located at 13q14. In such cases, a further genetic RB1 lesion in a neural retinal cell produces the tumour.[22] Infants with hereditary retinoblastoma present earlier compared with non-hereditary cases, are prone to bilateral disease and are at risk of second malignant neoplasm, particularly if treated with external beam radiotherapy. Usually, enucleation is curative for unilateral, sporadic retinoblastoma. In an attempt to preserve vision and reduce the risk of second malignant neoplasm, chemotherapy and local ophthalmic treatment (cryotherapy, laser photocoagulation, plaque radiotherapy) is used for bilateral disease.[21] Overall survival from retinoblastoma is excellent.

Retinoblastoma is exceedingly rare in AYA and older adults – 23 cases are reported.[23] In some cases the cancer may originate within a "benign" retinocytoma. All cases reported are unilateral; one would suspect the disease to be non-hereditary with the absence of a germline RB1 mutation. However, the author treated an infant with bilateral (hereditary) retinoblastoma whose mother was diagnosed with unilateral retinoblastoma as an adolescent – the infant and mother were shown to harbour a germline RB1 mutation. In AYA and adults, the most common presenting features are loss of vision and squint, present for a median of 16 months prior to diagnosis. Ocular examination reveals leucocoria and a "whitish" mass on fundoscopy – the differential diagnosis includes lymphoma, melanoma, metastatic carcinoma, retinocytoma and inflammatory diseases of the retina.[23] In contrast with infants, retinoblastoma in older patients is often not calcified. Diagnosis and treatment involves enucleation. If retinoblastoma is diagnosed in an AYA, referral to a specialist retinoblastoma service is recommended. Particular histological features (eg. progression along the optic nerve past the lamina cribrosa, choroidal infiltration particularly in conjunction with optic nerve involvement) are associated with increased risk of local and disseminated recurrence; patients with unilateral retinoblastoma displaying such features should receive adjuvant carboplatin, etoposide and vincristine.[24] Medical oncologists should be wary of a past history of hereditary/bilateral retinoblastoma – such patients are at risk of developing bone and soft tissue sarcoma, particularly if prior treatment included external beam radiotherapy.[25]

New Zealand AYA Cancer Service

Beginning in the late 1990s, a cancer control strategy was developed in New Zealand to prioritise and coordinate cancer related services, across the spectrum from prevention to palliative care. Objective 4 (goal 3) of the New Zealand Cancer Control Strategy aims to improve the quality of care delivered to adolescents with cancer and their family;[26] this objective was subsequently prioritised for inclusion in the Action Plan 2005-2010[27] (documents available at www.moh.govt.nz/cancercontrol). As a result, a working party was formed within the Ministry of Health – disciplines represented are medical and radiation oncology, psychology, haematology, surgery, nursing, adolescent medicine and paediatric oncology. Work is centred around the development of service specifications which bind District Health Boards to minimum standards of care. The principle is to provide treatment as close to home as possible, yet applying the highest standards of care. The objectives are to: improve the cure rate of AYA with cancer; maximise entry on to age-appropriate clinical trials; and provide optimal, age-appropriate psychosocial support.

A national AYA Cancer Steering Group will coordinate the service delivered in three regions across the country, each with a larger centre incorporating a child cancer unit, and smaller centre eg. in the South Island, the smaller centre in Dunedin is "twinned" with the larger centre in Christchurch. AYA cancer key workers are employed in each of the six centres, coordinating the provision of age appropriate care. Within each centre is a designated AYA cancer clinical leader linked to dedicated psychosocial and clinical trials support. Each AYA with cancer is to be managed within a multi-disciplinary team; those from the smaller centre are supported by linkage to the larger centre using videoconferencing. Importantly, this approach does not rely on the creation of AYA cancer units, but rather fosters a collegial and trusting relationship between adult and paediatric clinicians, concentrating on the broad interests of the AYA patient and their family.

Conclusion

In general, embryonal tumours of childhood are associated with a worse prognosis when they occur later in life. For low-stage Wilms' tumour and embryonal rhabdomyosarcoma, prognosis is improved when treatment is delivered according to paediatric guidelines. However, it is likely that differences in biological behaviour have a significant impact on tumour aggression. Whenever possible, AYA with embryonal tumours should be entered on to age-appropriate clinical trials:

- Uniformity of treatment will permit identification of clinical prognostic variables.
- Analysis of tumour material will elucidate the genetic mechanisms responsible for the greater aggression of these tumours.
- Evaluation of the toxicity of treatment – evidence suggests that AYA experience more side-effects from chemotherapy compared with children.

Finally, the care paradigm for AYA with embryonal tumours, involving close cooperation between adult and paediatric oncologists, should provide the blueprint for cooperative management of AYA cancers in general.

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