Surveillance of second cancer after previous childhood cancer treatment

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BACKGROUND
With the introduction of new therapeutic strategies, the survival of children and adolescents with cancer has increased dramatically. However, cancer survivors often experience late effects from their cancer treatment.

OBJECTIVE
A case study is presented that highlights the wide range of issues that may be encountered in young cancer survivors and underscores the necessity of continued follow up in this group of patients.

DISCUSSION
Risk factors and the recommended surveillance of second cancer in this group of patients are discussed.

Case study
Ms KM, 33 years of age, has a past history of Ewing sarcoma at L3 vertebrae diagnosed at 8 years of age which was treated successfully with 54 Gy external beam radiation and subsequent dacarbazine, doxorubicin (total dose of 435 mg/m^2) and vincristine chemotherapy. She has remained in remission of the Ewing sarcoma, but developed shortened trunk height with obvious muscle atrophy and cutaneous teleangiectasis within the irradiated field. A dysplastic appearing naevus in the irradiated field had been locally excised. She was otherwise well with ongoing follow up at the late effects clinic of the Peter MacCallum Cancer Centre with monitoring of anthracycline toxicity. In 2003, she smoked approximately 20 cigarettes per day and was a binge drinker of alcohol with up to 10–15 standard drinks on weekends. She was on sickness benefits but was previously employed with a design company.

Currently, almost 80% of children and adolescents with cancer can be cured of disease.[1] However, the cure may be accompanied by a host of late and often permanent complications arising from treatment. A recent review[2] provided an overview of the late effects of treatment for childhood cancer. The case study highlights the wide range of issues that may be encountered and how general practitioners, with additional input from specialists, can provide ongoing care for young cancer survivors.

Ms KM presented to our surgical unit in 2003 after an incidental finding of an 83x70 mm well defined encapsulated mass in the left lobe of the liver in a routine surveillance computerised tomography (CT) scan of the prior irradiated area. The lesion was anterior to the vertebrae in the path of radiation beam. She was asymptomatic with no history of liver cirrhosis. Alpha-feto protein level was normal. Liver function tests and albumin level were unremarkable with no coagulopathy. Hepatitis serology was negative. Ultrasound guided biopsy of the lesion confirmed presence of abnormal cells suggestive of well differentiated hepatocellular carcinoma or adenoma. F-18 FDG PET scan showed a centrally photopenic and peripherally metabolically active mass compatible with hepatocellular carcinoma with no evidence of extrahepatic disease. Diagnostic laparoscopy with laparoscopic ultrasound revealed a smooth lesion in segment II with no invasion of surrounding portal structures. The presumed diagnosis was of hepatocellular carcinoma.

During the laparoscopy, Ms KM had frequent ventricular ectopics with a brief run of ventricular tachycardia. She

was reviewed postoperatively by a cardiologist. Echocardiogram confirmed significant cardiomyopathy related to anthracycline chemotherapy with mild left ventricular dilatation and an ejection fraction of 35%. She was commenced on carvedilol and ramipril. In August 2003, she underwent left lateral hepatectomy without complication and postoperative recovery was unremarkable. Histology was consistent with a diagnosis of hepatic angiomyolipoma, an unusual but clinically borderline malignant tumour likely induced by previous radiotherapy. Repeat imaging did not reveal any residual or recurrent disease and she remains in remission 3 years later.

Ms KM has continuing follow up at the late effects clinic with regular structural imaging to detect further second cancer from previous chemoradiotherapy. Her creatinine level will be checked annually due to the possibility of long term renal impairment from scatter radiation dose to her kidneys. In addition, she will be monitored for potential premature menopause as a result of chemotherapy. Regarding her cardiac function, she has New York Heart Association (NYHA) class I-II symptoms and is taking ramipril, carvedilol, aldactone and frusemide with good tolerance and continues to see her cardiologist. Ms KM had considered becoming pregnant and saw a gynaecologist to evaluate her fertility. However, she is at high risk of decompensated heart failure during pregnancy and transplantation is relatively contraindicated because of two previous malignancies. She has decided not to proceed with pregnancy and has undergone tubal ligation.

Psychologically, Ms KM suffers from mild depression but responds well to antidepressant medication. With the ongoing support of her GP, she has ceased smoking and reduced her alcohol intake. Recently, she returned to employment and remains a highly functioning individual.

Discussion

With the advances in cancer treatment, it has

Table 1. Risk factors and recommended surveillance for common second cancers after previous chemoradiotherapy

Second cancer	Risk factors[9]	Surveillance for this cancer[9]
Breast cancer	• >20 Gy radiation to the thorax (eg. mantle, mini-mantle, mediastinal, thorax, axilla) • Female • Treatment during 10–16 years of age • Family history of breast cancer In patients <25 years of age who have had radiotherapy to the thorax there is an estimated incidence of 35% by 40 years of age which continues to increase[8]	• Latent period >5 years • Yearly breast examination from puberty until 25 years of age, then every 6 months • Mammography beginning 8 years after radiation or 25 years of age (whichever occurs last) NB: additional imaging modalities such as breast ultrasound should be considered in premenopausal patients if indicated
Bone cancer	• Treatment during puberty • Radiation exposure of >30 Gy combined with alkylating agents[10]	• Latent period >3 years • Yearly examination of the irradiated area followed by imaging (eg. plain radiograph, bone scan, CT or MRI) if indicated
Thyroid cancer	• Radiation to head and neck (eg. cranial, nasopharyngeal, oropharyngeal, cervical spine, supraclavicular, mantle, mini-mantle, total body irradiation) – risk increase up to 30 Gy with a downturn after 30 Gy[11] • Young children (<5 years of age) • Female	• Latent period 5–10 years[11] • Yearly thyroid examination • Ultrasound and fine needle aspiration to evaluate any palpable nodules
Brain cancer (benign/malignant)	• Radiation to the cranium, orbit, ear, infratemporal and nasopharyngeal region • Young children (<6 years of age) • Ataxia telangiectasia	• Yearly examination to identify any cognitive, motor and sensory deficit, seizures or other neurological symptoms • Brain MRI for symptomatic patients
Acute leukaemia	• Peak incidence 4–6 years and 1.5–3 years after initial treatment for alkylating agents and epipophyllotoxins respectively • Risk returns to baseline if no disease developed within 10 years[12]	• Yearly physical examination • Full blood examination • Follow up should be performed up to 10 years after initial treatment

emerged that cure may be accompanied by a host of late and often permanent complications arising from previous cancer treatment. While the majority of childhood cancer survivors would have been cared for by a specialist in the early stages of their disease, over time most of these patients drift away from specialty clinics as they become adults. It has been reported that less than 20% of adult survivors of childhood cancer are followed up at a cancer centre or by an oncologist and the likelihood of follow up with a specialist decreases over time.[3] General practitioners are therefore in an important position to monitor late effects of cancer treatment and provide ongoing health care for young cancer survivors.

Studies have shown that cancer and its treatment predispose to late morbidity and increase the risk of early mortality in childhood cancer survivors. Oeffinger et al[4] found that in 10 000 survivors with a mean age of 26.2 years (range 18.0–48.0) 62.3% reported at least one chronic health condition such as second cancers (eg. breast, colorectal, melanoma), cardiovascular disease, renal dysfunction, musculoskeletal problems and endocrinopathy (eg. premature gonadal failure, thyroid disease, osteoporosis, hypothalamic and pituitary dysfunction). Young survivors are also more likely to die prematurely. In a retrospective cohort study of 20 227 5 year survivors, Mertens et al[5] found a 10.8 fold excess in overall mortality. Risk of death is higher in females, children diagnosed with cancer before 5 years of age, and those with primary central nervous system tumours or leukaemia. Second cancer, cardiac and pulmonary sequelae accounted for 20% of deaths and the increased risk of mortality associated with treatment related sequelae persisted up to 25 years after initial treatment.

Second cancer is one of the well recognised late effects of cancer treatment. Subsets of patients exposed to radiation therapy or to specific chemotherapy agents and patients with known genetic predisposition were shown to be at higher risk for the occurrence of second cancer. Radiotherapy is the most important risk factor. The relative risk of developing second tumour in an irradiated field is 4.3 (95% CI: 3.0–6.2)[6] with 10–20 year latency. Some chemotherapy agents not only potentiate the carcinogenic effects of radiotherapy but can also contribute to the development of second cancer such as acute myeloid leukaemia, bladder and endometrial cancer. Children who carry genetic predispositions such as Li-Fraumeni syndrome (p53), hereditary retinoblastoma (Rb1), or neurofibromatosis (NF1) are at a higher risk of second neoplasms.

The most common second tumours are breast and bone cancer. Increased numbers of cancer was also observed in the central nervous system and thyroid, as well as leukaemia. The average median time to occurrence of second cancer was 11.7 years.[7] Studies have identified the risk factors of developing certain second cancers. *Table 1* summarises the risk factors of developing some of the most common second cancers and recommended surveillance strategies.

Childhood cancer survivors may also experience long term educational, behavioural and social impairment requiring early intervention and ongoing support from their GP and allied health providers. Hudson et al[13] found that childhood cancer survivors were more likely to report adverse mental health, activity limitations and functional impairment compared to their siblings. Risk factors include being female, those with a low income, low education achievement, a diagnosis of bone tumour, central nervous system tumour, sarcoma, or Hodgkin disease.[13] Modifiable behavioural risk factors such as tobacco cessation, moderate alcohol intake, exercise, and weight management should be emphasised as childhood survivors are especially vulnerable to many age related chronic health conditions due to previous treatments.

Conclusion

Childhood cancer survivors may experience a wide range of late effects from intensive cancer therapy, some of which remain clinically silent for long periods before becoming apparent. Young survivors and their families should be educated about their cancer treatment and associated health risks. General practitioners, together with specialists, play an important role in the long term surveillance for physical and psychosocial sequelae and in assisting patients reduce modifiable behaviour risk factors. Early intervention can improve the health status of young cancer survivors and reduce their overall morbidity and mortality. Periodic evaluations should include psychosocial and physical assessment for medical and emotional sequelae that may require further management.

Conflict of interest: none declared.

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