Childhood Cancer
9. Issues affecting survivors of childhood cancer after treatment

There are more than 11 million survivors of paediatric cancers living in the US alone in 2011 (Winick 2011). We do not have the figures for the UK. Many family's lives are totally disrupted by the emotional, time and energy consequences and stress of coping with the treatment itself, the physical and emotional needs of the patient and those of everyone else concerned. For these reasons, as well as to prevent the suffering that goes with the diagnosis of any form of cancer, it is important that the factors involved in the causation of childhood cancer become better known and prevented wherever possible. Many forms of childhood cancer can be treated effectively, some with a very high percentage chance of a 'cure' at least for several years. The longer-term consequences of surviving childhood cancer are, however, not always well known, and recommended risk-based care is not always available (Nathan 2008). These are very good reasons for preventing the cancer in the first place.

Some treatments, such as hematopoietic cell transplantation (HCT), seem to lead to more health complications later on, with unrelated donor HCT recipients being at highest risk. HCT survivors were more likely than sibling controls to have severe/life-threatening and two or more chronic health conditions, as well as functional impairment and activity limitation (Armenian 2011). CNS irradiation to temporal regions were associated with a higher risk for memory impairment, and more social and general health problems, whereas exposure to frontal regions was associated with general health problems and physical performance limitations (Armstrong 2010).

A study by Lorenzi (2011) found that survivors of childhood cancer, especially leukaemia, CNS tumours, bone & soft tissue sarcomas and kidney cancer, were at increased risk of many types of illnesses requiring hospitalisation, approximately 41% as against 17% of the general population. According to Winick (2011), the group most severely impacted by their cancer and their therapies are the survivors of CNS tumours.

Low-grade glioma survivors suffer many adverse effects, including blindness, hearing loss, obesity/overweight, hyperinsulism, growth hormone deficiency, thyroid hormone deficiency, and adrenocorticotropic hormone (ACTH) deficiency. Armstrong (2011) found that among 5-year survivors assessed for intellectual function, 34% had an IQ below average, associated with younger age at diagnosis, epilepsy and shunt placement.

The late effects of therapy for childhood leukaemia include secondary malignancy, cardiotoxicity, obesity, endocrine abnormalities, reproductive changes, neurocognitive deficits and psychosocial effects (Fulbright 2011, Bardi 2011).

Cancer recurrence

The duration and intensity of maintenance chemotherapy may influence the risk of subsequent cancers (Schmiegelow 2011). The risk of therapy-related myeloid neoplasms is below 2% for most series of treatments. This is important for younger cancer patients and during the first 5 years after the primary malignancies (Leone 2011).

An increased risk of secondary cancers and cardiovascular disease up to 20 years later was found in survivors of childhood Hodgkin lymphoma (Bhatia 1996) and Wilms tumour (Castellino 2011, Termuhlen 2011). Bhatia found the risk was higher in those treated between the ages of 10 and 16. Reulen (2011) found an excess risk associated with subsequent cancers in patients older than 40

years was for digestive and genitourinary neoplasms. Also indicated were risks of developing CNS tumours, nonmelanoma skin cancers and bone and breast cancer.

Some develop a different form of leukaemia following treatment for T-ALL (Szczepanski 2011). Szczepanski found that germline genetic abnormalities might contribute to a susceptibility to develop T-ALL.

Pettorini (2008) suggests that the infantile brain has a specific vulnerability, compared with adults. Children are more likely to develop radiation-induced cerebral tumours within 8 years of central nervous system irradiation. Radiation-induced tumours are correlated with higher levels of brain irradiation, over 80% at some distance from the maximum irradiation field. Nearly 74% were adult at the time of diagnosis of the radiation-induced tumour and 75% within 18 years after irradiation (Vinchon 2011). Risks of radiation-related cancer are greatest for those exposed early in life, and these risks appear to persist through life (Kleinerman 2006).

Kleinerman suggests that childhood cancer patients with inherited cancer syndromes, such as retinoblastoma, neurofibromatosis type 1, Li-Fraumeni syndrome and nevoid basal cell carcinoma syndrome are at substantial risk of developing radiation-related second and third cancers (2009).

Berger (2011) found that the risk of secondary cancers was highest after retinoblastomas, Hodgkin lymphomas, leukaemias, soft tissue sarcomas, CNS tumours and bone tumours. The authors felt that the follow-up time was too short to determine whether there were an increased risk of breast cancer (median follow-up time 9.8 years).

Radiation therapy for cancer increases the risk of developing subsequent thyroid cancer up to 14 or more times, depending on the therapeutic dose, sex (girls have a higher risk), age at exposure (the younger the child receiving the radiation, the higher the risk), and time since exposure (Bhatti 2010).

Reproductive effects

Fertility is decreased among female Childhood Cancer Survivor Study (CCSS) participants (Green 2009, 2011), though new approaches are being developed to preserve fertility with different methods to restore ovarian function (Hancke 2011).

It has been suggested (Levine 2011) that sperm banking for postpubertal males prior to gonadotoxic therapy should be considered as a matter of course. Postpubertal females receiving highly gonadotoxic therapy that places them at risk of acute ovarian failure should consider embryo or oocyte cryopreservation prior to the initiation of therapy. Females who receive treatment that depletes their ovarian reserve should be evaluated for the development of premature menopause following their treatment.

For childhood cancer survivors who maintain fertility, health risks to offspring resulting from their cancer treatment are major concerns. Radiation affecting ovarian and uterine function has been linked to pregnancy complications, including spontaneous abortion, preterm labour, foetal malposition and low birth weight. The risk of congenital malformations, genetic disorders and cancer appears to be low, with the exception of cancer risk in offspring born to survivors with germline cancer-predisposing mutations (Hudson 2010). Mueller (2009) found that infants born to female survivors of childhood and adolescent cancer were not at increased risk of malformations or death. Increased occurrence of preterm delivery and low birth weight suggest that close monitoring is warranted.

Total body irradiation (TBI)

TBI is still the most effective form of treatment for many paediatric malignancies. However, a significant number of cancer survivors go on to develop secondary malignancies following on from this treatment (Linsenmeier 2010, Kotecha 2011).

In a study by Felicetti (2011), 34% of patients receiving TBI showed growth hormone deficiency, Leydig cell failure was found in 23%, and elevated FSH levels, suggesting spermatogenesis damage was found in all patients. Primary hypothyroidism was more common.

TBI was also identified as a major risk factor for metabolic syndrome (Oudin 2011).

Other physical effects

There are many other physical health problems that are consequences of childhood cancer treatment.

The most commonly experienced ones are:

- Obesity - sometimes depending on gender, or type of cancer treated (Gurney 2003, Armstrong 2010, Pakakasama 2010, Breene 2011, Love 2011, Kohler 2011), especially in females. Robien (2008) suggests that there is a poor adherence to dietary guidelines, with too high a consumption of salt and sugar and inadequate whole grains, that may be at least partially responsible. CNS tumour survivors who are overweight are more likely to have complaints of excessive daytime sleepiness and are at greater risk of sleep-disordered breathing (Mandrell 2011).

- Reduced height - as a result of treatment for many cancers, especially brain tumours, depending on gender, age, and place needing treatment (Gurney 2003, Perkins 2007, Breene 2011). 25 years after diagnosis, ALL patients that were growth deficient experienced a significant decrease in Z-scores possibly suggesting a premature risk for osteoporosis. Growth hormone therapy was not shown to have a clear beneficial effect on bone mineral density, possibly the normal dose may be too low (Follin 2011), though it did achieve heights within the 'normal' range for some of the children, especially girls (Isfan 2011). GHRT carried no risk of recurrent neoplasms in a study by Mackenzie (2011), thus supporting the treatment following CNS radiation.

- Cardiac problems - cardiotoxicity is increased by chemotherapy especially in older girls. Survivors of childhood cancer should be monitored for the development of cardiac problems. Impaired artery flow is a risk following ALL treatment (Dengel 2008). It is unclear whether this relates to early development of cardiovascular disease. Cardiac side effects may progress over time and are a concern for patients treated during childhood. Most cardiovascular risk statistics and clinical experience are derived from patients treated before 1985, the modern radiation approach that limits the exposure of the heart and reduces the total dose seems to attenuate the previously observed cardiovascular risk (Yahalom & Portlock 2011).

Strokes are more likely in survivors of brain tumours (Bowers 2006, Gurney 2003). One of the most reported problems is sleep-wake disturbance, leading to decreased daytime alertness, possibly due to irregular melatonin secretion, following hypothalamic injury resulting from the brain tumour and its treatment (Gapstur 2009).

Restrictive lung disease was more frequently found after stem cell transplantation in childhood cancer survivors (Frisk 2011).

Late complications occur in many CNS tumour survivors. These complications include as well as hearing loss, blindness, cataracts, double vision, hypothyroidism, seizure disorders, need for medical induction of puberty, osteoporosis, cardiovascular conditions angina-like symptoms, ovarian failure and musculoskeletal (including co-ordination and motor control) problems, pulmonary abnormalities (Laverdière 2005, Packer 2003, Gurney 2003) and immune system dysfunction (Ek 2011). The majority of these are of mild-moderate severity, with only 4% being life-threatening (Laverdière 2005).

Bone mineral density is lower than expected in adult survivors of childhood ALL, specifically in men (Thomas 2008), depending on the treatment received (Le Meignen 2011). Nerve conduction abnormalities, including peripheral neuropathy were seen in nearly one third of children who had finished treatment for ALL more than 2 years previously (Ramchandren 2009).

Bone growth defects are associated with methotrexate, the most commonly used antimetabolite in paediatric cancer treatment (Fan 2011).

Therapeutic radiation has been associated with an increased risk for late mortality, pulmonary (Tantawy 2011), cardiac and thyroid dysfunction as well as an increased overall risk for chronic health conditions (Armstrong 2010). Children under 3 when treated with hematopoietic cell transplant (HCT) for ALL or AML were more likely to suffer from hypothyroidism, decreased bone mineral density, osteochondromas and dyslipidemias (increasing the risk of cardiovascular disease), & strokes (Perkins 2007, Gurney 2007).

Survivors had talked more often to a doctor than the general population, had increased hospital outpatient, day-patient and inpatient visits. Survivors of Hodgkin's lymphoma, neuroblastoma and Wilms tumour had the highest amount of day-patient care, whereas survivors of CNS tumours and bone sarcomas had the highest number of outpatient and inpatient visits. It did not vary significantly with age (Rebholz 2011).

Liver complications are common after treatment for childhood cancer. In a review of studies reporting hepatic effects, Mulder (2011) was unable to determine which part of treatment increased the risk.

According to Edelstein (2011), the most common health implication in survivors of childhood medulloblastoma were hearing impairment, second cancers, diabetes, hypertension and endocrine deficiencies. Adult survivors exhibit signs of early ageing regardless of how young they were at diagnosis.

Almost half of survivors of childhood leukaemia suffered from at least one effect (Pakakasama 2010) in a study from Thailand.

Childhood cancer survivors should have a thorough metabolic evaluation including the measurement of body fat percentage even if they are not obese. It has been suggested (Sohn 2011) that a better understanding of the determinants of the metabolic syndrome during adolescence might provide preventive interventions for improving health outcomes in adulthood.

Neurocognitive effects

Childhood leukaemia survivors performed poorly on measures of attention, girls worse than boys (Jain 2009). Krull (2011) suggests that attention problems similar to, but not typical of ADHD may be as a result of leukaemia-specific treatment.

ALL survivors tested significantly lower on verbal IQ and performance IQ 20 years after diagnosis, compared with healthy young adults, especially when treatment included cranial irradiation (Harila 2009). Anderson (2008, 2009) found a link between white brain matter damage and some of the more subtle neurocognitive late effects, such as difficulties with thinking and reasoning. The higher the dose of radiation and chemotherapy, and the younger the age at treatment, the more neurocognitive effects are likely (Edelstein 2011), especially evident on tasks involving rapid processing of information. Mabbott (2011) also found a significant decline over time in working memory, processing speed and visual memory in children who had been treated for CNS germ cell tumours.

Paediatric survivors of medulloblastoma were found to have a large decrease in cognitive capacity, including a slower acquisition of functions and knowledge in the domains of verbal comprehension, perceptual organisation, social perception and psychomotor skills (Saury 2011).

Significant numbers of cancer survivors had educational problems during schooling (Pakakasama 2010, Kuehni 2011). More survivors had compulsory age schooling only and fewer acquired a university degree. Survivors of CNS tumours, or those who had suffered a relapse, had poorer outcomes.

Survivors of infratentorial tumours (cerebellar) performed more poorly on selected measures of more specific cognitive functions and on parent-report of social-emotional functioning relative to survivors of supratentorial tumours (another type of cerebellar tumour). Higher frequency of auditory deficits was noted in the infratentorial tumour group and was associated with lowered academic achievement scores (Patel 2011).

Psychological and Social Effects

Substantial numbers of parents of children diagnosed with cancer experienced posttraumatic stress symptoms (PTSS), including depression and anxiety, during the first 6 months of treatment and after any relapse (Dunn 2011). 35% of survivors and 29% of their parents reported severe levels of PTSS (Bruce 2011).

During adolescence, survivors demonstrated higher rates of attention deficits, emotional problems, externalising behaviour and social withdrawal. These psychological problems are associated with an increased risk for obesity and poor health behaviour in adulthood (Krull 2010).

Quality of life

Long-term neuroblastoma survivors, especially those with hearing loss, are at greater risk of having academic learning problems and psychosocial difficulties. This is reflected in the child reporting loss of quality of life, due to the stress this causes (Gurney 2007). Adult survivors report that emotional well being continues to be affected into adult life (Nathan 2007), though Zebrack (2004) found the levels of psychological stress very similar to that of the general population.

Adult survivors of cancer with onset during adolescence experience less life satisfaction than the general population, and are less likely to live independently (Kunin-Batson 2011). The problems include psychological distress, somatic late effects and a lack of posttraumatic growth (Seitz 2010), and in another study included anxiety and depression as well (Seitz 2010). Ness (2008) reported that those survivors of childhood cancer who were worse affected were less likely to be employed, married, or have incomes greater than $20,000 a year. They were also likely to have problems getting health insurance. Emotional health limitations had the most impact.

However, some studies have shown high health-related quality of life (HRQoL) scores in childhood survivors and reduced indices of depression, especially those with more severe late effects and intensive therapy (Harila 2010, 2011). Perhaps pre-morbid personality differences play a part, or possibly support and after-care services available to patients, families and carers.

Hudson (2003) found that adult survivors of childhood CNS tumours were likely to report problems with adverse general health, mental health, activity limitations and functional impairment. The impact is aggravated by perceived shortcomings of long-term follow-up (Hovén 2011).