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Paediatric Update

Commentary

D.M. Green[a,b,*]

[a]*The Department of Pediatrics, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA*
[b]*Department of Pediatrics, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA*

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The prognosis for children and adolescents with cancer has improved dramatically. Recent data from the Surveillance, Epidemiology and End Results (SEER) programme of the National Cancer Institute (NCI) demonstrate that the overall 5-year survival rate increased from 55.7% for the period 1974–1976 to 77.1% for the period 1992–1997 [1]. Similar data have been reported for the United Kingdom [2]. It has been estimated that there was one childhood cancer survivor for every 900 persons in the general population of 15–44 year olds in the year 2000 [3].

As the percentage of patients with cancer diagnosed during childhood or adolescence who survive has increased, there has been interest both by former patients themselves and their physicians in research regarding the late medical effects of cancer therapy, and the impact they may have on the quality of life of those who have been successfully treated. Issues of particular concern to patients include the impact of their cancer therapy on their lifespan, their fertility and their offspring.

In their Update, Drs Jenney and Levitt review the concept of "quality of life", pointing out that it is multidimensional and may be measured from one of several perspectives, including those of the patient and the parent. Several cancer-specific measures have been developed, including the Miami Pediatric Quality of Life Inventory, the Pediatric Cancer Quality of Life Inventory, the Pediatric Oncology Quality of Life Questionnaire [4]. However, most of these have been validated only in children and adolescents, so their usefulness for the evaluation of the quality of life of adult survivors of childhood cancer is limited.

Quality of life involves an intersection between the physical, mental and spiritual domains. Drs Jenney and Levitt review most of the more frequent adverse effects of treatment on the physical and mental domains. Mental capacity may be damaged by exposure of the developing brain to radiation therapy or chemotherapy. Most of the literature that details radiation therapy 'late effects' has been derived from the follow-up of children treated for brain tumours or acute lymphoblastic leukaemia (ALL). Physicians anticipated that the elimination of cranial irradiation from the management of children with ALL would significantly reduce the percentage with residual adverse central nervous system effects. However, recent reports suggest that chemotherapy, without any whole brain radiation therapy, may also produce serious changes in central nervous structure and function [5]. More research will be necessary to identify those treatments least likely to produce central nervous system damage in patients with an extremely low risk of meningeal leukaemia, while continuing to refine prognostic factors used to identify those at greatest risk of this complication. Physicians, parents and educators should be aware that therapy may adversely impact intellectual capacity, attention and other functions that may require detailed evaluation and effective intervention.

Death more than 5 years after diagnosis is most frequently the result of progression or recurrence of the original cancer. However, when the patient survives for 5 or more years without tumour recurrence, the most frequent causes of late mortality are treatment-related cardiac disease, pulmonary disease and second malignant tumours [6–8].

Cardiac disease is the result of direct myocardial irradiation and/or treatment with one or more of the anthracycline antibiotics (doxorubicin, daunorubicin, epi-doxorubicin). Myocardial irradiation may occur as the result of whole lung or mediastinal irradiation, or when the left upper abdomen is irradiated. The relative risk (RR) of death due to acute myocardial infarction was 41.5 (95% confidence interval (CI) 18.1–82.1) among patients less than 21 years of age treated at

* Tel.: +1-716-845-2334 (business); +1-716-689-6372 (home); fax: +1-716-845-8003.
E-mail address: daniel.green@roswellpark.org (D.M. Green).

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Stanford University for Hodgkin's Disease [9]. Radiation-related valvular disease is now recognised with increasing frequency, and the aortic valve is most often involved [10,11]. Symptomatic disease may not appear until 7–39 years after mediastinal irradiation [11]. Anthracycline cardiomyopathy is thoroughly reviewed by Jenney and Levitt. Despite the universal recognition of factors that increase an individual's risk for the occurrence of anthracycline cardiomyopathy, there are unfortunately no universally recognised standards for the follow-up of such patients at present, nor do we have results from adequately powered randomised trials to guide follow-up recommendations [12–15]. This is a high priority area for clinical research.

Several factors including hyperlipidaemia, hypertension, cigarette smoking and obesity may interact with radiation- or anthracycline-related cardiac disease. Obesity was first reported as a late effect of 'prophylactic' cranial irradiation by Zee and Chen [16]. Didi and his colleagues reported that obesity was present in just under one half (45% of males and 47% of females) successfully treated for ALL when they were evaluated at the time of achievement of final height [17]. Others reported that 17–44% of those evaluated 4 years after cessation of therapy were obese [18]. This high incidence is in itself, a cause for real concern, as regards the future long-term health of these patients.

Second malignant neoplasms (SMNs) are a major cause of morbidity and mortality for survivors of childhood and adolescent cancer. Neglia and his colleagues reported that the RR of a SMN was 6.38 (95% CI 5.69–7.13) among members of the Childhood Cancer Survivor Study cohort. The largest RRs were for bone and breast SMNs. In a multivariate analysis controlled for radiation exposure, female gender ($P<0.001$), childhood cancer at a younger age ($P<0.001$ for trend), the diagnosis of Hodgkin's Disease ($P<0.001$) or soft-tissue sarcoma ($P=0.01$), and alkylating agent exposure ($P=0.02$ for trend) were all significant variables [19]. 'Second tumours' are discussed in detail in an Update in this series [20] by Dr Anna Meadows, with a Commentary by Dr Mike Hawkins [21].

The maintenance of health among survivors of childhood and adolescent cancer requires regular follow-up by physicians aware of the adverse effects produced by cancer treatment. However, few organised programmes for prolonged surveillance of adult survivors of childhood cancer exist in the United States [22]. It is apparent to paediatric oncologists, and those other physicians who have chosen to devote their clinical research efforts to adult survivors of childhood cancer that there are insufficient evidence-based data upon which to recommend follow-up strategies. Thus, follow-up recommendations are made empirically [23,24].

In general, we have adequate descriptive epidemiology regarding many of the complications of treatment for cancer in childhood and adolescence. In the future, resources should be devoted to the conduct of well-designed prospective trials of screening or intervention strategies that have sufficient statistical power to demonstrate whether a particular manoeuvre has reduced either mortality or morbidity.

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