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# Cure at what cost?

Michael C.G. Stevens [1]

*Academic Unit of Paediatric Oncology, University of Bristol, United Kingdom*

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The progress made over the past 30 years in improving cure rates for children with cancer has been remarkable, but this success has been achieved at a cost. An increasing number of young people, and now adults, who have survived cancer in the early years of life face the challenge – actual or potential – of long-term consequences of their disease and its treatment. Treatment related consequences include specific organ damage (cardiotoxicity, nephrotoxicity and others); growth and endocrine disruption; neuro-psychological damage; and second malignancy. Most of these problems can be correlated with exposure to specific treatment modalities and may be dose related. Their importance is reflected in the emerging patterns of morbidity and mortality seen in survivors and there is now an impressive body of the literature documenting such 'late effects' which are wide-ranging and variable in their significance [1]. In addition, it is recognised that the overall treatment 'experience' may impose a more generally adverse outcome by its interaction with factors such as social functioning, educational achievement and family dynamics [2].

Initially, reports of late, treatment related sequelae were based on observations in selected populations. These early studies may have under or over estimated the true incidence and nature of such problems but more recent investigations, particularly those from the Childhood Cancer Survivors Study (CCSS) in the United States [3], and, it is hoped, from a parallel project in the United Kingdom (the British Childhood Cancer Survivors Study – BCCSS) [4], will provide information from more representative populations. These data continue to clarify our understanding of the challenges facing survivors and offer useful guidance towards the modification of current treatments. The current state of knowledge, and opportunities for intervention, has been comprehensively reviewed by Ginsberg and Womer [5]. Nevertheless, some challenges remain in relation to the acquisition of such data, and in its application to clinical practice. It may be important also to consider how host factors could influence treatment related complications.

## 1. The need for long-term follow up

Many complications of treatment for cancer are acute and can be expected to recover after treatment is complete. Here, the challenge is to identify and introduce interventions that will facilitate the tolerance of treatment and contribute to an optimal outcome. In this respect, there is usually an assumption that long-term problems are unlikely and that the therapeutic 'risk' is almost entirely related to the acute situation. The risk of such complications, for example, myelosuppression, infection and nutritional compromise, has been increased as treatments have become more intensive but the development of better supportive care strategies has undoubtedly contributed to the improvements seen in cure. More difficult, however, is the scenario in which a treatment may have a limited or undetected acute impact but carry long-term potential for morbidity. The typical example is late cardiotoxicity after exposure to anthracycline agents where the likelihood of an acute problem occurring during treatment is known to be very small indeed yet even patients who show no abnormality on monitoring during therapy may be at risk of a late cardiac event. It is clear therefore that the scale and nature of such problems can only be evaluated by recruiting survivors to long-term follow up programmes.

*E-mail address:* m.stevens@bristol.ac.uk.

[1] Present address: Institute of Child Life and Health, 6th Floor, Education Centre, Upper Maudlin Street, Bristol BS2 8AE, United Kingdom. Tel.: +44 117 342 0205; fax: +44 117 342 0193.

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The study of survivors, therefore, should be recognised to be both patient and research-directed. In the first context, the intention is to identify, treat and/or prevent problems in individual survivors. In the second context, prospective observation of all survivors is undertaken to document risks, to explore interventions, and to identify target groups for future monitoring. It is also clear that patient directed care cannot evolve without the information derived from prospective observation of those who may (or may not) be at risk. This, in turn, raises a number of practical questions. Is indefinite follow up and ongoing monitoring always in the patient's best interest? Who should undertake such care? And who should pay (a question perhaps more immediately of concern in North America, but increasingly relevant elsewhere)? New models of care must be developed to balance the needs of the individual against the requirement to study the population recognising that it is as important to minimise the potential for inducing anxiety and over dependence in an individual as it is to facilitate ongoing data collection across the population of those at risk [6].

## 2. The problem of historical information

It is inevitable that, if some of the issues confronting the survivor of cancer in childhood may not emerge (or become relevant) until adult life, there may be a long interval between period of treatment and the time at which relevant information becomes available about that treatment. This means that problems now being encountered in adult survivors will reflect exposures to treatments which were current at least 15–20 years previously. These may no longer be in use, or, more likely, will have been substantially modified. Yet this information is essential to the design of new treatment strategies and to assist the 'trade-off' required to balance efficacy against toxicity. The historical 'gap' inevitably impedes our efforts to modify current therapy in an attempt to avoid possible late effects, particularly if risk factors are incompletely understood.

## 3. Individual risk

Although much has been learned about patterns of late toxicity, considerable inter individual variation is apparent amongst populations of survivors who have received the same treatment. Ginsberg and Womer, for example, highlight the fact that the risk of symptomatic anthracycline cardiomyopathy is a function of many variables. Prominent amongst these are factors such as cumulative dose, age at treatment and mode of administration. Nevertheless, the question remains, why do some individuals experience clinical symptoms when others do not, even when their exposure to probable risk factors is the same? Could there also be an element of individual predisposition? Some clues to this may reside in the observation that gender, race and diagnosis of Trisomy 21 may each have some impact on the risk of cardiotoxicity [7]. The identification of a predictive 'risk' genotype would be a substantial contribution to this field, allowing clinicians to better assess the risk to benefit ratio of the use of anthracycline and perhaps to target potential interventions at the time of treatment.

Further exploration of the factors determining individual risk is worthwhile but these may be difficult to unravel. The cause of any difference observed between individual patients may reside in factors active at the time of treatment delivery and may also influence treatment response. Progress in pharmacogenetics may offer opportunities not only to better understand lack of tumour response but also to identify patients at particular risk for toxicity [8]. Most of the investigations undertaken so far have focused on acute toxicity. For example, it is well established that mutations in the thiopurine methyltransferase gene (TPMT) can have an important impact on treatment tolerance and dose intensity in the maintenance treatment of children with acute lymphoblastic leukaemia (ALL) [9]. Further work, has suggested that germ line polymorphisms may relate to outcome in childhood ALL [10] but could this, and other mechanisms, have relevance for late effects of treatment? There is interesting data to suggest that pharmacogenetic risk factors may identify patients with acute lymphoblastic leukaemia at particular risk for the development of treatment related osteonecrosis [11]. Reduced inactivation of doxorubicin (and cyclophosphamide) reactive oxygen species, which occurs as a consequence of variability in glutathione-*S*-transferase (GST) activity, confers improvement in tumour response [12], but could this also imply an enhanced risk of late cardiotoxicity?

The suggestion that individual genetic polymorphisms can influence disease outcome, presumably by modulating the efficacy of chemotherapy, needs to be explored in the context of the risk of late effects of treatment. The concept of pre existing genetic susceptibility is better understood in the aetiology of second malignancy where it is recognised that patients with certain primary genetic conditions (*e.g.*, Neurofibromatosis type 1) and those with other established cancer predisposition defects (*e.g.*, hereditary retinoblastoma, Li-Fraumeni syndrome) are at especial risk of treatment related second cancer. There is also evidence that mutations in systems such as those involving GST may predispose individuals to secondary leukaemia [13]. The systematic evaluation of the relevant genetic information could, in time, contribute to the creation of an individual profile of biological efficacy and toxicity, and may help identify patients at special risk.

## 4. The future

Ginsberg and Womer are correct in pointing out that much remains to be understood about the factors that influence late effects of therapy. Yet without an improved knowledge base, strategies designed to avoid or to ameliorate specific late toxicities can not be easily identified, evaluated or implemented. Improvements in the cure of children and young people with cancer owe much to the culture of collaboration and clinical trials on which paediatric oncology is based. The call for the same systematic evaluation of the challenges facing survivors is both timely and essential.

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