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CURRENT TOPIC

Childhood cancer: cure at what cost?

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'The cost of a thing is the amount of what I call life which is required to be exchanged for it immediately or in the long run' (Thoreau, 1854).[1]

Twenty years ago, cure, a return to health or being made sound or whole, was contemplated for less than a quarter of all children who developed malignant disease and indeed was a word rarely used. The dramatic improvements in survival seen for the majority of types of cancer in childhood have led to a situation where we can with some confidence predict that if a child has survived five or more years with no evidence of malignant disease then recurrence is unlikely. Late relapses do occur but these are becoming less common with modern treatment.[2 3] Long term follow up has shown that although the majority of children are survivors, many have significant sequelae resulting from their successful treatment. These late effects can therefore be taken as the price that has had to be paid to achieve long term survival. When assessing the whole cost benefit equation the costs of treatment and its effects on the child and his family must also be taken into account.

The overall cure rate for childhood cancer in the United Kingdom is now over 60% and for some groups more than 90%. One in 600 children develop cancer before their 15th birthday so that by the year 2000 at least one in 1000 young adults will have been cured of cancer as children.

Optimum treatment, giving the child the best hope of survival with the least chance of late sequelae, requires initial referral to a specialist centre. Stiller has recently shown that survival for most types of cancer and leukaemia is significantly better for those referred to such centres,[4] and even when survival rates are very high in non-specialist hospitals these apparently good results have been achieved using outdated treatments that have a greater risk of side effects.[5] Surgery, chemotherapy, and radiotherapy may all be required and these along with a high intensity of nursing and other professional support lead to paediatric oncology being a high cost service. It has been estimated that the average total cost of hospital treatment for a child with cancer is £45 000.[6] Added to this must be the considerable financial costs to the family,[7] particularly when their home is many miles distant from the regional referral centre, as well as the psychological disruption and trauma involved.[8]

The costs of treatment are usually furthest from a family's mind when the initial diagnosis is made and all they want is the current best available treatment and very few question the ethical aspects of treatment, and talk of long term side effects are of little importance. In the weeks after diagnosis parents have a chance to learn more about the long term prospects and it is often at this stage that the implications of infertility and other side effects begin to be questioned. They rarely request less toxic treatment, however, but it is possible that guilt feelings are heightened.

The long term sequelae of successful treatment may be due to any of the three modalities of therapy currently used. Surgery may be mutilating with obvious physical sequelae, for example amputation, or more subtle, for example nephrectomy for Wilms' tumour. Radiotherapy produces permanent damage to any normal tissue within the irradiation field and the degree of effect is dose and age related and can result in long term consequences at any site in the body. The late effects of treatment can be categorised according to the system considered.

Endocrine consequences

Shalet *et al* have recently reviewed the endocrine consequences of the treatment of malignant disease.[9 10] Much endocrine dysfunction is the late consequence of radiotherapy but several cytotoxic drugs are also damaging and in most cases can be predicted from a knowledge of the dose-effect relationship. Pituitary damage resulting in growth hormone deficiency and subsequent growth failure is a common result of the treatment of brain tumours where a high dose of radiotherapy is necessary to effect a cure whereas the lower dose of irradiation given to treat occult central nervous system leukaemia may lead to physiological abnormalities of growth hormone secretion but less often results in overt growth failure. Growth problems may be exacerbated in those who receive spinal irradiation because of a direct effect on the growing vertebrae.[11] Precocious puberty is also well recognised after cranial irradiation.[12] Thyroid damage after radiation to the neck for Hodgkin's disease or for spinal tumours occasionally results in overt hypothyroidism but more commonly this is compensated for by a high thyroid stimulating hormone drive.[13] Gonadal dysfunction in both sexes can be the result of irradiation but boys show more overt evidence of damage due to chemotherapy. This may be due to a better power of recovery of the ovary when compared with the testis.[14 15] A recent study from Australia has shown that

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whereas primary gonadal dysfunction occurs in both sexes this is compensated for by increased concentrations of luteinising hormone and follicle stimulating hormone, which in girls can lead to early puberty.[16] Early menopause is being increasingly recognised in very long term survivors of childhood cancer, and this is almost certainly due to a loss of germ cells often secondary to irradiation.[17]

Renal dysfunction

Renal dysfunction may result from surgery—for example, nephrectomy for Wilms' tumour—irradiation or chemotherapy. Hypertension is being recognised at late follow up for Wilms' tumour and renal failure secondary to long-standing hyperperfusion of the remaining kidney has been reported.[18] Cisplatinum, which is being increasingly used for the treatment of childhood cancer, can cause significant glomerular damage,[19] and the alkylating agent ifosfamide produces tubular dysfunction.[20] These drugs have not been in use long enough to know whether the renal damage caused is either progressive or reversible. Renal toxicity may be exacerbated by the use of aminoglycoside antibiotics that are commonly used to treat infections during episodes of neutropenia.

Cardiovascular effects

Hypertension may be seen but the most serious problem is found in children who have been treated with the anthracycline group of drugs, which are well recognised to be cardiotoxic.[21] The cumulative dose at which significant cardiac dysfunction is likely to occur is now well known and current practice would prevent doses larger than this being given. Even when doses have been limited and cardiac function as measured has seemed normal, however, sudden cardiac decompensation does occur and this may be secondary to the stress of, for example, viral myocarditis or pregnancy.[22]

Neuropsychological sequelae

These sequelae appear to be limited to those children who have received cranial irradiation either for brain tumours or acute lymphoblastic leukaemia.[23] Those irradiated below the age of 2 years appear to have the worst outcome.[24] Much thought has been given to alternative methods of treating occult central nervous system disease in children with acute lymphoblastic leukaemia. Recent protocols have reduced the dose of irradiation from 24 Gy to 18 Gy but it is too soon to know whether this will reduce the incidence of learning difficulties. Prolonged intrathecal drugs or high dose methotrexate may be equally effective, and less toxic, although one recent study showed no difference in the incidence of learning difficulties in those given irradiation or high dose systemic chemotherapy.[25] The next Medical Research Council UKALL trial is addressing this issue of trying to find an equally effective but less toxic form of central nervous system treatment.

Fertility

Direct irradiation to the gonads in either sex usually causes infertility and even low dose scatter irradiation can be damaging. The ovary seems better able to withstand the effects of chemotherapy. Most girls who survive will be able to conceive but boys, especially those who have been treated with alkylating agents—for example, cyclophosphamide—are likely to be infertile. Many babies have now been born to mothers or fathers who had cancer as children, however, and fortunately there seems to be no increased risk of congenital abnormalities or of cancer in the offspring.[26 27] More studies need to be carried out before a definitive statement can be made about outcome of all pregnancies in that there is a suggestion that there may be an increased miscarriage rate especially in those who have received irradiation. Early menopause does occur in girls,[17] and those wishing to become pregnant should be encouraged to do so sooner rather than later.

Secondary primary tumours

The development of a second malignancy in a child surviving malignancy has been recognised increasingly in recent years.[28 29] Initially many of these were either skin cancers or bone or soft tissue sarcomas arising within irradiated fields but now secondary primary tumours are being seen after most types of cancer even where irradiation has not been used. Some of these tumours are in patients with known genetic predisposition (for example retinoblastoma) but others may result from chromosomal damage caused by the treatment for the initial malignancy. The cumulative incidence of secondary primary tumours has been studied in a large international cohort of survivors and appears to be in the order of 3% at 15 years from diagnosis. Many of the patients in this cohort had orthovoltage irradiation, which is known to be more likely to cause secondary primary tumours than the more modern megavoltage so that this may be seen less in the future. However, the additive effects of chemotherapy have yet to be assessed.

Immunity

Both chemotherapy and radiotherapy can suppress immunity but for practical purposes it can be considered that the child's immune state will have returned to normal six months after completion of treatment or one year after a bone marrow transplant. It has recently been reported, however, that long term damage occurs to haemopoietic stem cells with potential for malignant transformation.[30]

Social problems

The long term impact of having a child with cancer can break up families and induce significant behaviour problems in siblings. The child himself may have considerable problems in adult life. He or she may have difficulty obtaining life insurance and mortages and be at a significant disadvantage in seeking employment. There continues to be much ignorance

and inaccurate information manifest in the lay public and, more distressingly, by medical advisors to large industries and institutions. They often have an erroneously pessimistic view of probable mortality rates and give uninformed advice. However, it should be noted that not all survivors of childhood malignancy know that they have had cancer. A recent study from the United States showed that 14% of survivors were unaware of their initial diagnosis.[31] With the current trend towards more open communication this is not likely to be so in the future.

Litigation

Although not a problem yet in the United Kingdom, the problems of physicians being sued because of late effects in adults successfully treated for cancer in childhood is beginning to happen in the United States.[32] Those treating children with cancer must be aware of this potential for legal action and ensure that informed consent is obtained for all treatments where the late effects are known but unavoidable.

Childhood cancer would therefore appear to be expensive to treat and have a catalogue of potential serious long term sequelae. Is it worth it? The true incidence of such late effects in a complete cohort of children is not known. A multinational study of 20 000 long term survivors is currently being planned and this should give a clearer idea of the magnitude of the problems. Any such study by its very nature must be historical, however, and apply only to treatment given to that particular cohort. The continued recognition of late effects has led to modification of current protocols of treatment to try and lessen the long term sequelae while not compromising survival rates.

The need for long term follow up and evaluation of sequelae of treatment in a population of patients apparently cured of their original disease may appear obvious in retrospect but even now many young adults are discharged from surveillance. Follow up must be forever. This should be carried out by clinicians who are prepared to face their mistakes and investigate the causes carefully. The natural delight and satisfaction of mutual success must not be allowed to distort the overall analysis of results. Medical audit is particularly important in this field where progress is rapid.

A carefully planned assessment of all aspects of potential problems is essential if the correct management of these patients is to be continued in adult life. Physicians working in the adult field do not encounter the same problems and are not attuned to the appropriate response. In terms of 'man years' saved children cured by the age of 5 or 6 years have 70 years or more of useful life to count on. Many children have survived at a price but most would consider it a price worth paying, but their carers cannot sit back with complete satisfaction.

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