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Malignant disease in childhood: The price of cure
Late physical and socioeconomic effects of treatment

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ABSTRACT: The aim of cancer therapy in childhood is to achieve a lasting cure without physical and psychosocial harm and, preferably, at a low financial cost. Although cure is possible in many types of childhood cancer, this is often accompanied by complications as a consequence of intensive therapy. These late effects primarily affect fertility, the cardio-respiratory and endocrinological systems. Psychosocial adverse effects may have serious implications on the marriage and employment prospects of those patients surviving into adulthood. Furthermore, the risk of treatment-induced, secondary malignancies may increase as survival improves. With current intensive chemotherapy and radiotherapy, the attainment of cure rates in excess of 60-70% is, inevitably, associated with significant morbidity. Indeed, recent developments in cancer therapy have focused on ways of reducing this morbidity, whilst still maintaining the overall improvement in survival.

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Introduction

Long term cure, as opposed to short or medium-term survival, is presently a reality in up to 60% of children with malignant disease [1,2]. Currently, 1 in 2,000 twenty year olds is a survivor of childhood cancer and this figure is estimated to climb to 1 in 1,000 by the early part of the 21st century[1]. The improved prognosis for many children with cancer has followed intensive clinical, pharmacological and molecular biological research spanning the past thirty years. This research, administered via controlled, internationally co-ordinated trials, has resulted in significant improvements in paediatric cancer therapy. Nevertheless, the reality of a cure has been achieved with an increase in treatment-related morbidity, both in the acute phase of therapy as well as long term. This paper reviews the late physical and psychological effects of current therapy for childhood cancer, and highlights the financial implications of achieving a cure for cancer.

Late effects of cancer and cancer therapy

As patients live longer, more late effects are recognised, some of which predominantly involve specific systems (Table 1) whereas others are still poorly defined (e.g. libido, employment). Individual late effects may follow chemotherapy, radiotherapy and surgery.

Cardiovascular sequelae

Anthracyclines (e.g. doxorubicin, daunorubicin) are important agents in commonly used chemotherapeutic protocols for childhood leukaemia and solid tumours. Yet they are well recognised cardiotoxic agents, the toxicity increasing with cumulative dose and rapidity of their infusion[3]. They usually result in a cardiomyopathy which may improve on discontinuation of the drug (with the risk of a diminished anti-cancer effect), but which can result in intractable heart failure[4] requiring transplantation (observation). Sudden cardiac decompensation may be precipitated by pregnancy, infection and strenuous exercise, even in those thought to have normal cardiac function. Indeed, all patients who have received anthracyclines should be carefully monitored during pregnancy. Arrhythmias, usually with a prolonged Q-T interval and supraventricular ectopics, are less common, but may result in sudden death [5]. Radiotherapy at a dose >30Gy to the mediastinum involving the heart may exacerbate functional valvular dysfunction, predispose to premature coronary disease and increase the risk of infarction in later life [6]. Radiotoxicity, like chemotoxicity, is also dose related.

Table 1 - Systems involved in late effects of childhood cancer

Commonly affected	*Rarely affected*	*Ill defined*
cardiovascular	gastrointestinal	neurological
endocrine	respiratory	psychological
reproductive	special senses	socioeconomic
musculoskeletal	renal	secondary-malignancy

These sequelae have altered paediatric oncology practice such that the total dose of anthracyclines is carefully recorded and infusion times increased to 4-6 hours from bolus injections. Their complete omission is likely to result in a significant risk of relapse, and current work is focusing on the simultaneous administration of cardioprotective agents [7]. However, these expensive agents may reduce the efficacy of anthracyclines [7] and,

together with routine cardiac assessments with ECG and echocardiography, will increase the financial cost of treatment. The role of additional radionuclide functional cardiac scans is unclear but would further escalate the cost of follow up.

Respiratory sequelae

Complications of cancer therapy involving the lungs are unusual. Pulmonary fibrosis may develop following bleomycin and high dose radiotherapy (>30Gy), whereas whole lung irradiation results in small volume lungs with normal gas diffusion [8]. The latter is associated with a mild to moderate decrease in exercise tolerance, in contrast to the severe handicap manifest by patients who develop pulmonary graft versus host disease (GVHD) after allogenic bone marrow transplantation or donor lymphocyte infusion for relapsed leukaemia (observation). Modern treatment protocols with restricted use of lung radiotherapy for widespread metastases in refractory Wilms' tumour, and aggressive immuno-suppression against GVHD have reduced the incidence of these debilitating pulmonary sequelae. Nevertheless, total body irradiation (TBI) has a deleterious effect on alveolar growth and, when administered to young children prior to bone marrow transplantation, can result in pulmonary hypoplasia after a number of years.

Endocrine sequelae

Intensive chemotherapy and radiotherapy result in major late complications involving linear growth, pubertal development, fertility and thyroid function. These sequelae are particularly severe in those who receive combination therapy, especially involving allogenic bone marrow transplantation (Table 2) [9].

Table 2: Endocrine sequelae after allogenic bone marrow transplantation (BMT)

Sequelae	*Indication for BMT*	
	Non malignant	*Malignancy*
survival	: 80%	20-70%
growth	: normal	impaired
hypothyroidism		
- compensated	: 8%	18-35%
- overt	: <2%	8-11%
thyroid neoplasia	: 0%	1.7%
puberty, menarche	: normal	delayed
ovarian dysfunction	: <5%	20%
azoospermia	: 50%	100%
Leydig cell function	: normal	impaired

Effects on growth

Hypopituitarism is common after surgery for hypothalamic tumours, and after radiotherapy for cranial tumours and CNS-directed treatment for leukaemia. The anterior pituitary is primarily affected, usually resulting in growth hormone (GH) deficiency and short stature. The precise mechanism of GH insufficiency following cranial radiotherapy is unclear but may be related to a reduction in GH-releasing hormone (somatostatin), which is associated with disorganised GH secretion and low amplitude GH peaks. The latter is exaggerated at puberty, when the normal surge in GH release does not occur. Indeed, 100% of patients who received 30Gy involving the pituitary are GH deficient five years later. The damage and, therefore, subsequent loss in final height, is dose related [10] and more severe in young patients [11,12], especially those irradiated for a brain tumour rather than leukaemia [13]. GH deficiency is generally isolated and develops within two to five years after treatment. Panhypopituitarism is less common, with deficiencies in TSH, gonadotrophin releasing hormone and lastly ACTH presenting over a period of several years.

Chemotherapy not only exacerbates GH deficiency after radiotherapy but, in isolation, has been shown to reduce more than 1SD in height in 32% of patients at one year, and up to 71% at six years [14]. This effect may be due to the adverse effect of intensive chemotherapy on the growth plate [14,15], which is supported by in vivo observations but, as yet, remains unclear during in vitro studies.

Once confirmed, growth hormone deficiency requires GH replacement by subcutaneous injection, approximately five to seven times a week. GH may prevent further height loss but the final height achieved may still be suboptimal since GH may be less effective in patients who also have truncal shortening due to spinal irradiation [16]. The loss in spinal growth is worse in younger patients and may be as much as 9cm with irradiation at one year versus 5.5cm at ten years [16]. Furthermore, treatment with a growth-promoting, potentially mutagenic, agent such as GH may increase the risk of second malignancies [17,18].

Careful radiotherapy planning, and accurate targeting, if necessary under daily general anaesthesia, may help reduce pituitary damage. In patients 'at risk', GH replacement should be anticipated, and confirmed by suitable GH-provocation tests. In order to reduce the risk of second leukaemias, GH treatment is not commenced until two years have elapsed from the initial cancer treatment.

Growth can also be adversely affected by direct radiation damage to bone, malnutrition, steroid therapy and, in children who received an allogenic bone marrow transplant, by graft versus host disease.

Effects on puberty

Precocious puberty is common, especially in girls who received cranial radiotherapy at a young age [19]. This results in early closure of the epiphyses [12] and, together with blunting of the normal surge in GH during puberty, further exacerbates the problem of short stature [20]. Unless growth during puberty is closely monitored, an initial but inadequate growth spurt may mask underlying poor growth velocity. Once impending short stature is realised, treatment with GH must commence before menarche is established. Nevertheless, GH may be less effective in these patients unless combined with a gonadotrophin-releasing hormone analogue in order to arrest pubertal maturation.

Effects on reproduction

Infertility in male survivors is common since several chemotherapeutic agents disrupt the germinal epithelium, resulting in small testes and azoospermia [21,22]. This damage is dose dependent, particularly with alkylating agents (e.g. cyclophosphamide), and especially when multiple chemotherapeutic agents are administered to younger boys [12,22,23]. Leydig cell function, on the other hand, is rarely compromised and in 96% of cases, androgen replacement is not necessary[23]. In girls, the ovary is relatively chemotherapy-resistant and ovarian steroidogenesis is generally preserved [15,24]. Although inhibition of follicular maturation may result in premature menopause, the prospects for fertility are good. In a study of 40 girls treated for ALL, all progressed through puberty, 37 had normal menses and 9 gave birth to 14 children without congenital anomalies or malignant disease [24].

Radiotherapy administered directly to the testes causes germ cell ablation, fibrosis, azoospermia and infertility, as well as impaired Leydig cell function requiring androgen replacement [25]. The testes remain infantile in size [21], but the effect on libido remains difficult to quantify [21-23]. The LD50 of the human oocyte is <4cGy and ovarian radiotherapy causes a net loss of oocytes and impaired oestradiol production, resulting in delayed/arrested puberty, amenorrhoea and infertility [26]. Oestrogen replacement is necessary to maintain secondary sexual characteristics, prevent osteoporosis and decrease the risk of ischaemic heart disease. Involvement of the uterus in the radiotherapy field disrupts its growth with a poor reproductive outcome. Indeed, these patients have an increased risk of mid-trimester miscarriage, premature delivery and low birth weight infants. Furthermore, they are not suitable candidates for in-vitro fertilisation with donor oocytes since the uterus does not produce a satisfactory endometrial response to sex steroid replacement [26].

Patients with a history of intensive chemotherapy and/or pelvic or scrotal radiotherapy require regular clinical assessment of sexual maturation, together with measurements of FSH, LH, testosterone and oestradiol. A blunted response to human chorionic gonadotrophin stimulation will confirm gonadal hormonal failure and prompt androgen/oestrogen replacement. Male infertility is confirmed by azoospermia on semen analysis. Pretreatment sperm banking (at diagnosis) often produces a poor yield and is not widely available. In view of the serious psychosocial consequences of infertility, all affected patients should be offered professional counselling. Reassurance can be offered to those who had cancer in childhood and who retain fertility, since there is no increased risk of treatment-induced congenital anomalies or cancer in their offspring[27].

Effects on thyroid function

Although the precise impact of chemotherapy on the thyroid gland is unclear, its extreme susceptibility to radiotherapy is unequivocal. Thyroid dysfunction including hypothyroidism compensated by a high TSH drive, may develop within 12 months from radiotherapy[28]. Overt hypothyroidism usually develops in 66% of patients within three to six years of thyroid irradiation[28,29]. Earlier onset is observed in younger children and is proportional to increasing doses. Radiotherapy increases the risk of morphological abnormalities such as focal hyperplasia, thyroiditis, thyroid fibrosis and adenomas. The risk of carcinoma increases 100-fold, and occurs in up to 1.7% of survivors of cervical Hodgkins disease of the neck [29]. The risk is increased further in those with elevated TSH levels which persist for several years [29,30]. Thyroid carcinomas have been reported after a prolonged latency period (>13 yrs) and, in this setting, are invariably fatal. Hence, long term monitoring of TSH levels, thyroid ultrasound and isotope scans are indicated. Thyroxine replacement should be given to children with frank hypothyroidism, as well as to those with compensated thyroid dysfunction with the aim of returning elevated TSH levels to normal, thereby reducing the risk of thyroid carcinoma [2, 30].

Renal sequelae

Decreased glomerular and tubular function follow high dose ifosfamide and cisplatinum [31,32]. Renal dysfunction is exacerbated by aminoglycoside antibiotics, but recovery is usually complete in the majority of patients. Without the concurrent use of mesna, alkylating agents (cyclophosphamide, ifosfamide) can result in haemorrhagic cystitis leading to fibrosis and reduced bladder capacity.

Neurological sequelae

Cranial irradiation, especially to the developing brain before the age of two years, is associated with neuronal damage and, often subtle, neurodisabilities. Significant memory deficit may follow treatment for ALL [33] and the IQ may be decreased by as much as five to ten points following cranial irradiation [34]. Neuropsychometric deficit is usually greater with attention span and non verbal, cognitive skills so that these children have difficulty predominantly with mathematics and spelling. Given the slow rate of neuronal development, many of these effects are not manifest for several years. Indeed, the long term prospects for dementia as a result of irradiation-induced neurovascular damage in early childhood remains unknown.

Other physical sequelae

Hepatic fibrosis and veno-occlusive disease may follow the use of 6-mercaptopurine and busulphan, respectively. Auditory impairment is common in survivors of childhood cancer, often as a direct chemotoxic effect (e.g. cisplatinum), or secondary to ototoxic antibiotics (aminoglycosides). Visual impairment follows unilateral enucleation which is necessary in 50% of patients with retinoblastoma, or is secondary to global atrophy and cataract formation after radiotherapy. Asymmetrical atrophy of the face, trunk or limbs is a significant, permanent problem after wide field, intensive radiotherapy (e.g. for sarcomas), whereas gross disfigurement follows surgical amputation.

The use of mutagenic treatment modalities in susceptible individuals has led to an increasing number of reports of late secondary tumours [35]. These include radiotherapy-induced thyroid carcinoma and sarcomas in the peripheral area of radiotherapy fields, as well as

alkylating agent and etoposide-induced acute myeloid leukaemia. The risk of treatment-resistance in these secondary tumours is high, and they are invariably fatal.

Psychological and psychosocial sequelae

Although some families 'pull together' during a crisis, others may fall apart under the strain associated with a child with cancer. In this setting, behavioural problems in siblings as well as the patient, marital dysharmony and family breakdown, are not uncommon.

Not surprisingly, children who survive childhood cancer may carry feelings of anger (why me?), resentment (why not someone else?), guilt and frustration into adulthood. These, coupled with the metabolic complications, physical handicaps and reproductive deficiencies highlighted above, may result in poor self esteem and, at times, psychiatric illness including depression [1,2]. A poor ability to cope in society, rejection by peers, and diminished intellect will decrease the prospects for higher education. Ultimately the combination of physical and psychosocial problems dampen both the marital and job prospects of these patients. Indeed, in certain countries, some institutions (e.g. the armed forces) apply positive discrimination against their employment. Insurance may be a major problem - often it is simply not available or only offered at an extortionate premium.

Quality of life

Attempts have been made to quantify 'quality of life' of survivors of cancer [36], but such assessments are highly subjective and, at best, extremely crude. Most questionnaire-based surveys are able to gauge physical problems rather better than psychosocial 'handicaps'. Nevertheless, reports would suggest that, once children survive their malignant condition, their quality of life is no worse than their peers [36,37].

Monetary costs of treatment

Cost of acute treatment

Assuming treatment is completed with no untoward complications or excessive admissions, an estimate for a single child weighing 15kg with acute lymphoblastic leukaemia being treated on the current chemotherapeutic protocol is approximately Lm5,000 over 2.5 years (Table 3). The cost may be two to three times as much for those with solid tumours who may receive more intensive regimens (Table 3). With a mean of ten new and relapsed patients per year, this translates into an approximate annual expenditure of Lm50,000. Many of these patients are referred to hospitals in the UK with whom the Department operates a shared care programme, in order to complete treatment not available in Malta (e.g. bone marrow transplantation). If not for a reciprocal health care agreement between the two countries, these additional courses could inflate the annual cost to the Department of Health by two to three times, or more.

Follow up costs

To the 'acute' cost must be added imponderables such as the cost of follow-up, subsequent cardiac, endocrine and other investigations, and treatment of late effects. As discussed previously, the latter may not be inconsequential: e.g. the annual cost of GH replacement is approximately Lm1,000 per patient. Assisted fertility procedures may become standard treatment for these patients, but it is rather more difficult to provide for the unexpected, e.g. heart transplantation for those with intractable anthracycline-induced cardiomyopathy.

Table 3 - Monetary cost for treatment of childhood ALL and neuroblastoma

Cost in Lm * per patient (15kg)		ALL	neuroblastoma
Days in hospital	:	3,680	5,600
Drugs - cytotoxics	:	697	365
- antibiotics	:	194	484
- antiemetics	:	197	328
Investigation			
- blood	:	120	180
- imaging	:	50	250
Procedures			
- central line	:	49	49
- surgery	:	0	1,000 ***
- transplant	:	0 **	2,500 ***
TOTAL	:	4,987	10,756

** Costs are calculated on current prices pertaining to government services, July 1997.*

*** The estimate is for children with acute lymphoblastic leukaemia (ALL) in first remission, when bone marrow transplantation is not indicated.*

**** These estimates apply to treatment for neuroblastoma, which may include visits to the UK for surgery and peripheral stem cell or autologous marrow transplantation.*

Physicians have a duty to offer the 'best available' treatment and, at the outset, must inform parents of the late consequences of therapy. At diagnosis, the latter appear of little importance when compared with the chance of survival, but may invoke feelings of anger and guilt as years go by and the complications of treatment evolve. This raises the possibility of litigation proceedings against the health authorities by affected patients, a scenario that has become a reality in the United States, but not yet in Europe [1].

Measures to reduce late effects

Clearly, prevention is better than cure. Continuously improved drug regimens, dosage, and scheduling, refined radiotherapy and surgical techniques all contribute toward lowering the morbidity of cancer therapy. Specific protective agents (e.g. against anthracycline-cardiomyopathy) may become available during the acute phase of treatment. Nevertheless, late complications are inevitable and need to be anticipated in survivors. Once confirmed, prompt correction will reduce further long term morbidity. Finally, quality of life is further enhanced by improved aids (e.g. prostheses), and a better understanding of the problems facing these patients both by the physicians involved in their care, as well as by the general population.

Conclusion

Major advances in cancer treatment in childhood have resulted in an overall cure rate of approximately 60% of cases [38]. There is little doubt that the vast majority of childhood cancer should be treated. Management should entail modern chemotherapeutic regimens in order to effect the best chance of survival, with provision to anticipate and cater for treatment-induced early and late complications. The impact of late morbidity has been appreciated relatively recently, and unknown problems may yet arise. Hence, the reduction of late effects has become a major goal in cancer treatment, equalling efforts to improve overall survival.

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