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Original Paper

Cardiac Transplantation in Childhood Cancer Survivors in Great Britain

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The aim of this study was to identify patients treated in Great Britain for childhood cancer and subsequently referred for cardiopulmonary transplantation in order to assess diagnosis, cancer treatment, management and outcome. Computerised record linkage between the National Registry of Childhood Tumours and the national transplant database held and maintained by the United Kingdom Transplant Support Service Authority (UKTSSA) was used to identify patients. Verification and clinical details were then obtained from the oncology and transplant centres. 16 patients were identified from the 31992 cases of childhood malignancy diagnosed in Britain since 1970. These comprised 13 heart transplants, 2 heart/lung transplants and 1 patient who died while on the heart transplantation waiting list. All 14 potential heart transplant patients had cardiomyopathy presumed secondary to anthracycline therapy. The original diagnoses were acute myeloblastic leukaemia (3), Wilms' tumour (4), rhabdomyosarcoma (2) and one each of five different solid tumours. Median age at diagnosis was 44 months (range 4–165 months). Median anthracycline dose was 413 mg/m^2 (range 240–680 mg/m^2). 13 of the 14 potential cardiac transplantation patients were more than 2 years from end of their cancer treatment before requiring transplantation and the transplantation was performed 2–126 months after onset of cardiac failure at a median age of 163 months. Five year actuarial survival from transplantation was 74%. There was no recurrence of the original malignancy in any of these patients. Both heart/lung patients died, 3 and 11 months after the transplant. These heart transplantation data suggest that, in Britain, survival compares favourably with that of patients whose heart transplant was required for other causes of cardiomyopathy. This indicates that patients successfully treated for childhood cancer should not be excluded from transplant programmes.

Key words: heart transplantation, anthracycline, cardiomyopathy, childhood cancer
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INTRODUCTION

ANTHRACYCLINES AND, to a lesser extent, radiotherapy have been responsible for cardiomyopathy in survivors of childhood cancer [1,2]. The natural history of treatment-related cardiotoxicity is variable, but progression to irreversible heart failure will occur in a significant proportion of patients [3]. Cardiac transplantation is the only treatment that can improve life expectancy and quality of life in patients with end stage heart failure.

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Cardiac transplantation was first used in children in the mid 1980s, but its application was strictly limited by the supply of donor organs [4]. In addition, survivors of cancer with congestive cardiac failure were not considered ideal candidates because of the theoretical risks associated with the use of post-transplant immunosuppression. Relapse of the primary malignancy, second malignant tumour and an increased risk of lymphoproliferative disorders were cited as reasons for the reluctance to refer and accept patients on to transplant programmes. The first successful cardiac transplantation in a child with anthracycline cardiotoxicity was reported in 1988 [5]. Since then only one report on a small series of 3 paediatric patients from a single centre has been published [6].

Because of the rarity of this complication of cancer treatment, individual centres have little experience. The aim of this study was to accumulate data from all childhood cancer patients in Great Britain who had been referred for cardiac transplantation so that the causes, management and outcome could be assessed.

MATERIALS AND METHODS

Children below 15 years of age diagnosed with cancer in Great Britain are registered with the National Registry of Childhood Tumours (NRCT) [7] held in Oxford by the Childhood Cancer Research Group. The NRCT receives notifications from several sources (mean number of notifications per child: 2.25) and ascertainment is believed to be almost complete. Anthracyclines were not used in Great Britain prior to 1970, and thus only the 31992 NRCT cases diagnosed in 1970 or later were considered in this study.

The United Kingdom Transplant Support Service Authority (UKTSSA) holds and maintains the national database of transplantation in Britain, and has collated data from the 12 British cardiac transplant centres since 1984. This database identifies patients who have received heart or heart/lung transplants and those who have been on active waiting lists for such operations. There were 1501 patients, born after 1955, and registered with the UKTSSA in the period January 1985 to April 1994 (Figure 1).

Computerised record linkage was used to compare relevant records for the two data sources. The system used was based on the Generalised Iterative Record Linkage System (GIRLS) developed at the National Cancer Institute of Canada [8] and used probabilistic methods to assign a score to all appropriate comparisons of pairs of records from the two sources. This composite score was based on the outcome of comparing individual items of data such as surname, first name(s), sex, day, month and year of birth, taking into account the relative frequency of the values for each item. Pairs of records with a score at or above a preset level were then available for further consideration.

Likely matches were verified by obtaining medical histories from the oncology and transplant centres. For confirmed matches, information on cancer diagnosis, treatment, timing of occurrence of congestive heart failure (CHF) and outcome were obtained.

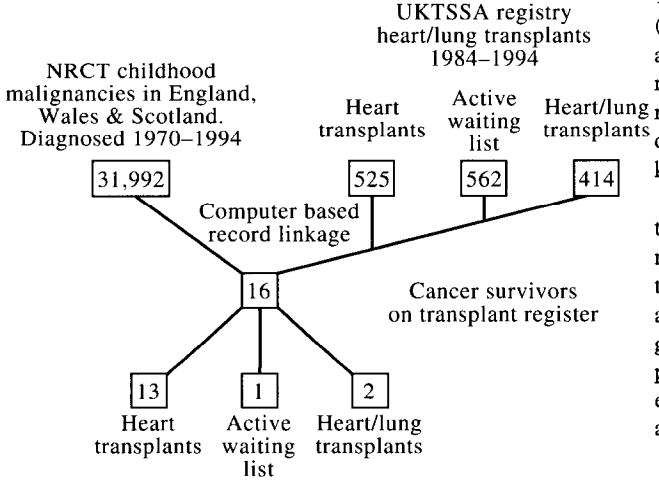

Figure 1. Ascertainment of patients. NRCT, National Registry of Childhood Tumours. UKTSSA, United Kingdom Transplant Support Services Authority Register.

RESULTS

Matched pairs of records relating to 16 patients were identified: 13 had received heart transplants, 1 died awaiting a heart transplant and 2 had received heart and lung transplants. Malignancies were diagnosed between 1973 and 1990 and cardiothoracic transplants were performed between 1984 and 1994. The heart transplant patients (HTI–HT14) will be considered initially: 4 were treated for Wilms' tumour, 3 for acute myeloblastic leukaemia (AML), 2 for rhabdomyosarcoma and the remaining 5 patients each had a separate tumour type (Table 1).

The median age of the original diagnosis was 44 months (range 4–165 months). All patients received anthracyline as part of their treatment with a median cumulative anthracycline dose of 413 mg/m^2 (range 240–680 mg/m^2). Patients with solid tumours received doxorubicin and the AML survivors received daunorubicin; in addition, 4 of the solid tumour patients received the potentially cardiotoxic drugs, cyclophosphamide (6–15 g/m^2), and 1 patient also received ifosfamide (80 g/m^2). Radiotherapy was given to 5 patients (Table 1). The radiation dose to the heart could not be calculated, but it was likely that the heart was within the field in at least 3 patients. 2 AML patients also received mitrozantrone.

The interval between cancer treatment and the presentation of CHF varied widely. There was a bimodal pattern with a median of 12 months (range 0–141 months). The interval bore no relationship to age at cancer treatment or to anthracycline dose.

Cardiac transplantation was performed from 2–126 months (median 52 months), after the initial presentation of cardiac failure. Of the 8 patients with early onset heart failure ($\leq$12 months from end of cancer treatment), 7 responded to antifailure treatment and received their transplants more than 48 months from presentation with CHF (range 52–126 months). Conversely, all the children presenting with CHF more than 12 months after completing cancer treatment (range 35–141 months) required transplantation at a median interval of 5 months (range 2–15 months).

The median age at transplantation was 163 months (range 111–272 months). The 5 year actuarial survival was 74% (Figure 2). Most survivors have enjoyed a good quality of life, attending school or university. 3 patients have died, one from multi-organ failure (1 month post operative (HT11), one from rejection after 11 months (HT13), and a third (HT12; original diagnosis neuroblastoma) died of acute lymphoblastic leukaemia at 41 months after transplant.

In addition, 2 patients required combined heart and lung transplantation for end stage pulmonary disease, 118 and 33 months from end of cancer treatment. One patient received thoracic radiation for treatment of a ganglioneuroblastoma and the other patient had suffered severe chronic pulmonary graft versus host disease after allogeneic bone marrow transplant for relapsed acute lymphoblastic leukaemia. Both patients died, 3 and 11 months after transplant, from rejection and sepsis, respectively.

DISCUSSION

This population-based review of cardiac transplantation for the relief of cancer treatment-related cardiomyopathy summarises the national experience of childhood cancer and the

Table 1. Patient characteristics, treatment and outcome

Patient no.	Diagnosis	Age at diagnosis (months)	Year of diagnosis	Sex	Treatment		Time from end of treatment to heart failure (months)	Time from heart failure to transplant (months)	Year of transplant	Outcome (survival in months)
					Total anthracycline mg/m²	Radiation cGy				
HT1	Wilms' tumour (L) Stage II→pulmonary relapse	47	1978	M	500	L Hemi abdomen L lung	141	6	1991	Alive (47)
HT2	Wilms' tumour (L) Stage III	57	1980	F	350	L abdomen 2000	115	2	1991	Alive (51)
HT3	Wilms' tumour (L) Stage III →pulmonary relapse	33	1983	F	240	Lung 1500, boost L lower lobe 4000	75	15	1992	Alive (36)
HT4	Wilms' tumour bilateral	36	1983	F	400		84	—	—	No donor organ found - died
HT5	AML	37	1982	F	500		86	4	1991	Alive (51)
HT6	AML	35	1985	F	480		11	89	1994	Alive (18)
HT7	AML	68	1990	M	300		35	5	1993	Alive (30)
HT8	Prostatic rhabdomyosarcoma	60	1981	M	470	Abdomen 4600	2	126	1993	Alive (23)
HT9	Facial rhabdomosarcoma	165	1984	F	335		2	3	1985	Alive (120)
HT10	Orchidoblastoma	4	1973	M	500		5	125	1986	Alive (106)
HT11	Oestogenic sarcoma	162	1975	F	680		5	92	1984	Died (1)
HT12	Pelvic neuroblastoma	22	1977	F	425	Pelvis	1	89	1985	Died (41)
HT13	Malignant histiocytosis	158	1982	M	300		0	52	1986	Died (11)
HT14	Hepatoblastoma	4	1984	M	285		12	83	1993	Alive (27)

AML, acute myeloblastic leukaemia; ALL, acute lymphoblastic leukaemia. Solid tumours, anthracycline–doxorubicin; leukaemia, anthracycline–daunorubicin.

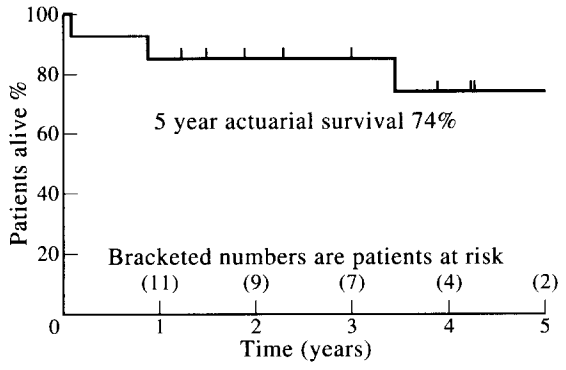

Figure 2. Survival after cardiac transplantation. Vertical marks refer to individual patients.

12 cardiac transplant centres. The use of national databases to identify patients should ensure that more such patients are identified than would be possible simply by relying on the recall of clinicians. The small number of patients requiring this treatment is reassuring, but this survey does not take into account patients not referred for cardiac transplantation. Additional information on the size of the problem comes from the paper by Robertson and associates [9] which reports on the late deaths (more than 5 years from diagnosis), in the same population as our study, between 1971 and 1985. Of the 9080 survivors, there were 4 patients who died of anthracycline-induced cardiomyopathy without reference to a cardiac transplant centre. The contribution to the prevalence of cancer treatment-related cardiomyopathy from the incidence of early onset end stage heart failure is unknown as it is not systematically reported in patients entering trial protocols (UKW1[10], UKALLX[11]). Currently, it is not possible to ascertain the actual incidence of severe cardiomyopathy as the denominator, i.e. the number of patients receiving anthracycline and/or cardiac radiation amongst British cancer survivors, is unknown.

All the patients reported here had received variable total doses of anthracycline with or without cardiac radiation. No patients were identified who received cardiac radiation without anthracycline. Radiation more commonly causes pericardial or coronary artery disease [2].

Wilms' tumour (HT1–HT4) was the commonest diagnosis and is probably a reflection of the high (>80%) survival rate [12] over the last 20 years. In addition to anthracycline treatment, 3 of these 4 patients had received abdominal and/or lung radiation with a significant radiation dose to the heart. Cardiac radiation, in association with drug therapy, has been shown to have an additive effect on the myocardium [13]. More recent protocols have incorporated a reduction in the anthracycline dose (U.K. protocol maximum dose 360 mg/m^2) and radiation use.

3 patients had AML, a worrying feature as only recently has the 5 year survival of this group exceeded 50%, and it may be difficult to alter treatment regimes and still maintain a high survival rate. These patients receive relatively high total anthracycline doses with high dose intensity and tend to be sicker throughout their treatment course than other groups. The latter to our knowledge has not been studied as a risk factor, but perhaps deserves consideration. The dose intensity has been shown to be a risk factor in cardiac studies on asymptomatic patients [14,15].

The median age at diagnosis of hepatoblastoma patients is only 18 months so they may be at increased risk of cardiotoxicity. The PLADO protocol used on patient HT11 included bolus doses of doxorubicin [16]. In the more recent Societé Internationale d'Oncologie Pédiatrique (SIOP) liver tumour study SIOPEL-1 protocol [17], administration of doxorubicin was by continuous infusion over 48 h in an attempt to reduce the risk of cardiomyopathy. Anthracyclines are now not included in protocols for the treatment of malignant germ cell tumours (HT10) or neuroblastoma (HT12), so the incidence of cardiotoxicity in these patients should plateau and then fall.

The onset of the critical phase of heart failure is variable, but in this small study it appears that patients presenting early, less than 2 years from end of treatment, can be sustained with antifailure treatment, and later may manage without treatment for many years before the critical phase of their illness ensues. The reverse seems to occur for those patients presenting many years from treatment: they require early transplantation. In either case, the ethical issue of presenting these patients for transplantation before they would be considered 'cured' is not a major problem.

The outcome of this series was encouraging (3-year actuarial survival after transplantation was 85%). Survival of 95% at 1 year and 87% at 3 years can be expected after transplantation for cardiomyopathy [18]. However, long-term morbidity may occur as the result of development of coronary artery disease and detrimental effects of immunosuppression therapy including renal dysfunction, opportunistic infections and neoplasms. There were no relapses from the primary malignancy which is reassuring and supports reports from renal transplant patients with pre-existing childhood malignancy [19,20]. These studies showed the risk of relapse is highest when transplantation is undertaken within 24 months of the end of cancer therapy. All our patients, except for one (HT-9), with good risk rhabdomyosarcoma, received their heart transplants at least 36 months after cancer treatment was completed. One patient, many years from transplant, died due to a second malignancy (HT-12). No patients had polyclonal lymphoproliferative disease. To date, there is no substantial evidence that the theoretical risk of failure due to immunosuppression has been realised. With many of the patients presenting several years after treatment, the magnitude of the problem will increase as more patients become long-term survivors. We cannot, therefore, be complacent and must continue to search for less cardiotoxic, but equally effective, cancer drugs or advocate the use of cardioprotective agents. However, there is no evidence that patients with cancer treatment-related cardiomyopathy should be withheld from referral to cardiac transplant centres.

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