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Paper

Allogeneic Bone Marrow Transplant in Belfast – An outcome overview of the first 25 years

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INTRODUCTION

The first sibling allogeneic bone marrow transplant in Ireland was undertaken in Belfast in December 1980. Up to March 2005 a total of 139 transplants were carried out mainly in the Royal Victoria Hospital but also in the Belfast City Hospital. Over 25 years the transplant unit has grown in both volume and experience with 42 patients having undergone transplant since the year 2000. Although representing a small proportion of transplants performed throughout Europe, both survival, morbidity and mortality rates have been found to be comparable to national and international averages. This study highlights both the remarkable changes in transplantation over time and the outcome of sibling allogeneic transplant in the major haematological illnesses.

BACKGROUND

Bone marrow transplantation (BMT) is currently an important treatment option in a variety of malignant and non-malignant diseases[1]. This practice began as a means of repopulating the haemopoietic stem cell compartment following myeloblative exposure to radiation as a means of 'rescue'. It has since evolved into a means to induce anti-tumour responses when used in malignancy[2].

BMT can be either autologous (the transferred haematopoietic stem cells (HSC) are obtained from the patient) or allogeneic (HSC are from a donor that is optimally, totally matched at the major histocompatibility complex loci)[2].

Classically, BMT involves some form of cytoreductive conditioning of the recipient with irradiation and/or chemotherapy. HSC were previously provided exclusively by bone marrow cells however other sources have shown efficacy including mobilised peripheral blood and more recently cord blood. Subsequent HSC engraftment requires immunosuppression[2].

Bone marrow transplant is, however, hampered by significant toxicities, which limit its efficacy. Graft versus host disease (GVHD) is ultimately the result of donor T cell attack on the immunocompromised and genetically dissimilar recipient resulting in multi-organ damage and morbidity[2]. These same T cells also seem to have graft versus tumour (leukaemia) effect as demonstrated by studies in which removal of T cells prevented GVHD but also increased relapse rates[2].

Further complications include a profound period of immune deficiency leaving the patient susceptible to opportunistic infections and donor graft rejection[2].

Unfortunately common means to prevent or treat GVHD with systemic immunosuppression (e.g. cyclosporin / corticosteroids) can lead to impaired immune recovery, increased opportunistic infections and higher relapse rates[2].

METHODS

Data was collected from both EBMT MED-B forms (forms submitted to EBMT containing transplant details and outcome) and patient records. Allogeneic transplants carried out between December 1980 and March 2005 of all ages were included. Ninety-eight percent of patients received bone marrow grafts from human leucocyte antigen identical siblings. Two were haploid identical grafts and one was an HLA phenotypic match. Information at time of transplant, including age, gender, diagnosis and date of transplant was recorded. Outcome following transplant was sub-divided into time frames – 100 days post transplant, 100 days to 5 years post transplant, 5-10 years post transplant and 10+ years post transplant. Outcome was measured by both morbidity and mortality with specific complications, disease status, and cause of death being recorded. Results for the four most commonly transplanted diseases – Acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia and aplastic anaemia – were further sub-divided to enable specific analysis in relation to disease status.

The data collected was ultimately compared to those noted in European and international databases. Information was gathered from the Centre for International Blood and Marrow Transplant Research (CIBMTR), the world's largest clinical database of related blood and marrow transplants, along with the European group for Blood and Marrow Transplantation (EBMT). Results obtained including demographics, survival, morbidity and mortality were subsequently compared to those in our centre to highlight similarities in outcome.

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RESULTS

Demographics

Of the 139 patients transplanted within this time frame 86 were male and 53 were female. The mean age was 29.8 years (overall range 5 – 58). The number of transplants carried out biennially over this time period has shown a significant increase from just 3 between 1980 and 1981 to 22 between 2000 and 2001 (fig 1). The most common underlying diagnosis in our unit was acute lymphoblastic leukaemia (ALL) with forty-five cases (33%) transplanted within this time period. Thirty-six patients (26%) had a diagnosis of acute myeloid leukaemia (AML), twenty-five (18%) of chronic myeloid leukaemia (CML), fourteen (10%) of aplastic anaemia, six (4%) of multiple myeloma and two (1%) of chronic lymphocytic leukaemia. The remaining eleven patients were classified as other diagnoses (Fig 2).

Overall Survival

Overall survival following transplant, calculated as those alive at time of analysis, was found to be 44.6% (62 patients). Seventy-seven patients (55.4%) were deceased. Overall median survival was 60 months. Ten-year transplant survival is shown in fig. 3. Of those that died, 42 were recorded to be secondary to treatment related mortality and 35 secondary to relapse. When subdividing treatment related mortality, graft versus host disease (GvHD) was found to be the most common underlying cause with 23% of deaths being secondary to either acute or chronic GvHD.

Graft versus Host Disease

Forty-seven patients in total developed acute GvHD (developing <100 days after transplant) while 32 patients developed chronic GVHD (>100 days). Acute GvHD was graded using the Glucksberg staging depending on the extent of skin, liver and gut involvement. Twenty-five patients were assessed as grade I (mild) or grade II (moderate), 22 were grade III (severe) or grade IV (life threatening). Of those with grade III or IV aGvHD only one patient is alive today. The majority of patients died as a subsequence of GVHD (90%). In contrast, almost half the patients with grade I or II aGVHD are alive today. Only one death, within this group, was recorded as secondary to GVHD.

This finding highlights the extensive mortality associated with GVHD particularly in grade III and IV disease.

Disease Specific Survival

Acute Leukaemia

Of those patients with ALL (45 pts), 38% were alive at time of analysis. Disease relapse accounted for the majority (64%) of deaths with 36% as a result of treatment related mortality (e.g. graft versus host disease, infection). Alternatively 50% of patients with AML were alive at the time of analysis with equal mortality rates from relapse and treatment related causes.

These results do appear to demonstrate an improved outcome after transplant in the AML group; however, it is important to note that the majority of deaths in the ALL group were secondary to disease relapse.

Chronic Myeloid Leukaemia

Those patients with a diagnosis of CML represented 18% of total transplants. Approximately half were alive at time of analysis (48%) with the majority of deaths being secondary to treatment related causes (92%). Interestingly a large number of patients developed both acute and chronic GVHD (44% and 37% respectively). It is well known that donor cells have the capacity to control residual leukaemic cells, a phenomenon known as the graft versus leukaemia reaction[3]. The lower incidence of relapse in this group along with a high incidence of GVHD highlights this effect.

Aplastic Anaemia

Fourteen patients with aplastic anaemia underwent transplant during this time period. Eight patients (57%) were alive at time of analysis with the longest survivor being 23 years from transplant. All deaths were treatment related and largely due to GVHD and infection.

DISCUSSION

Since the 1970s bone marrow transplantation has been used with increasing frequency in the management of both malignant and non-malignant diseases[1]. Interest in the effects of radiation on the body post-world war II, led to studies into the damaging effects on the bone marrow, with laboratory observations and animal studies forming the basis of transplant biology[1].

In 1956 first reports of attempts to treat humans with total body irradiation and marrow infusion were published[1]. Dr E Thomas, a haematologist based in Cooperstown, New York achieved a transient graft on a leukaemic patient in 1957[4]. In 1959 the same group reported 2 cases of isologous transplantation for the treatment of acute leukaemia on 2 children using marrow from their identical twin. Successful transplant was achieved with remissions of seven and twelve weeks[5]. Thomas later went on to receive the Nobel Prize for discoveries concerning organ and cell transplantation in 1990[4].

A French group achieved the first persistent transplant in a patient with acute lymphoblastic leukaemia, reported in 1965. The patient died 20 months after transplant from herpes zoster virus. Post mortem revealed no evidence of disease relapse[3]. Over subsequent years increasing knowledge of histocompatibility antigen systems led to the first successful allogeneic transplant using a sibling donor in 1968[6].

Since this time the use of bone marrow transplantation has increased substantially. Transplants for leukaemia in first remission or first relapse demonstrated a much-improved overall survival and subsequently this treatment was applied to a number of malignant and non-malignant diseases[1].

Surveys from the Centre for International Blood and Marrow Transplantation (CIBMTR) report a 630% increase in allogeneic transplants between 1981 and 1990[7]. Similar results were also noted from the European group for Blood and Marrow Transplantation (EBMT) data bank revealing an increase from 200 transplants in 1980 to 6065 in 1992[8]. Although this increase can be partly explained by better reporting and more complete data, this growth reflects the

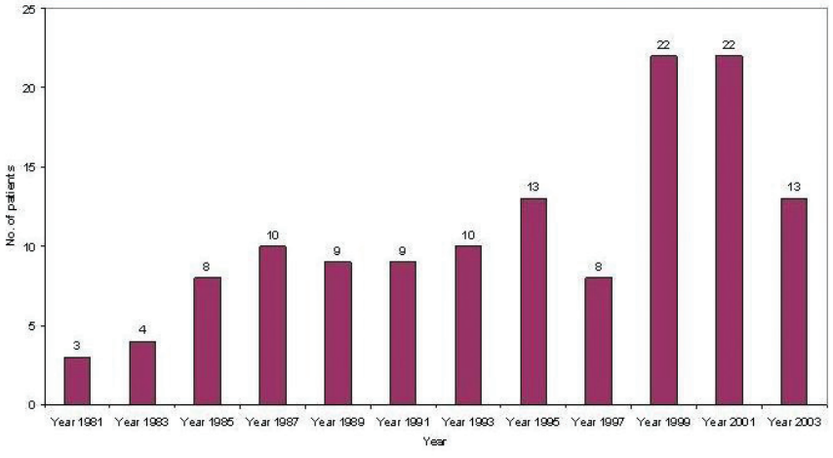


Fig 1. Number of Allogeneic transplants carried out over time

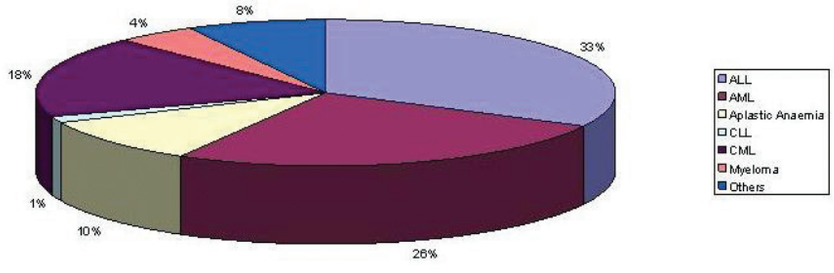


Fig 2. Primary diagnosis of those undergoing transplant in Belfast

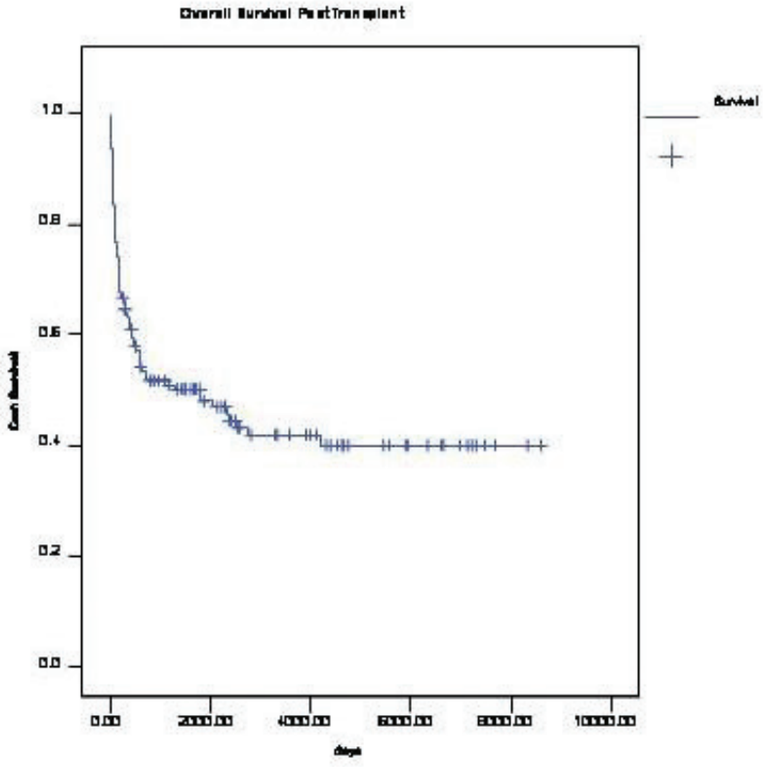


Fig 3. Overall probability of survival following transplant in Belfast

increase in units carrying out transplant.

The first allogeneic bone marrow transplant in Belfast took place in December 1980. The patient, a 12-year-old girl with ALL in her third complete remission, engrafted and survived beyond 100 days, however developed complications of both acute GVHD and pneumococcal septicaemia. This first transplant, nevertheless, led to the development of the successful BMT unit at the Royal Victoria Hospital, which transferred to the Belfast City Hospital in 2001. Since 1980, the frequency of transplantation in Belfast has also increased substantially with a 630% increase from 1980 to 2001 (Fig.1).

Further distinct changes over time have been noted in keeping with worldwide records. CIBMTR highlighted the increasing age of patients undergoing transplant with more patients over the age of 50 being transplanted as the procedure improved and progressed[9]. Again our unit showed similar results with an increase in patients over the age of 41 being transplanted from 1990, and the first patient over 50 to be transplanted in 2002 (Figs 4 and 5).

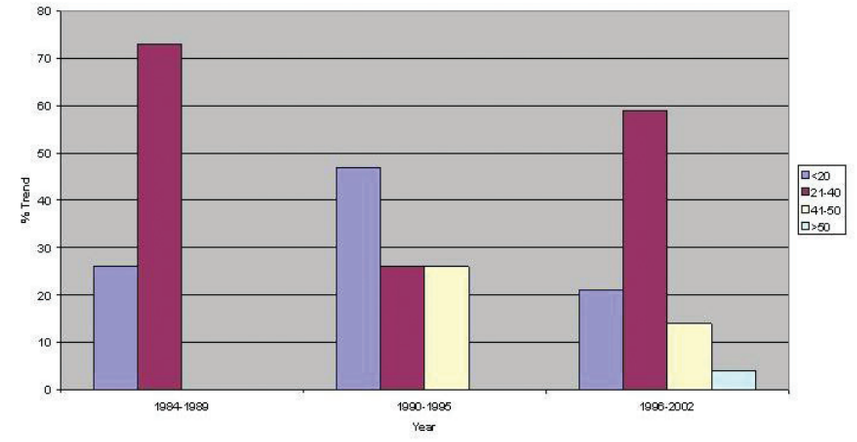
Between 1980 and 2005, the most common underlying disease requiring transplant in Belfast was found to be ALL (33%). This was followed by AML with 26% of the total patients transplanted suffering from this disease. The CIBMTR report a larger frequency of transplants for AML with nearly double the frequency of ALL transplants[9]. This is again noted in the British Society of Blood & Marrow Transplantation (BSBMT) register with ~ 30% of allo-transplants carried out for AML and 19% for ALL each year[10]. The reason for this is unclear though our sample size is small for comparison. Also prior to the year 2000 a larger proportion of patients with ALL were transplanted as at this time the numbers were inclusive of children.

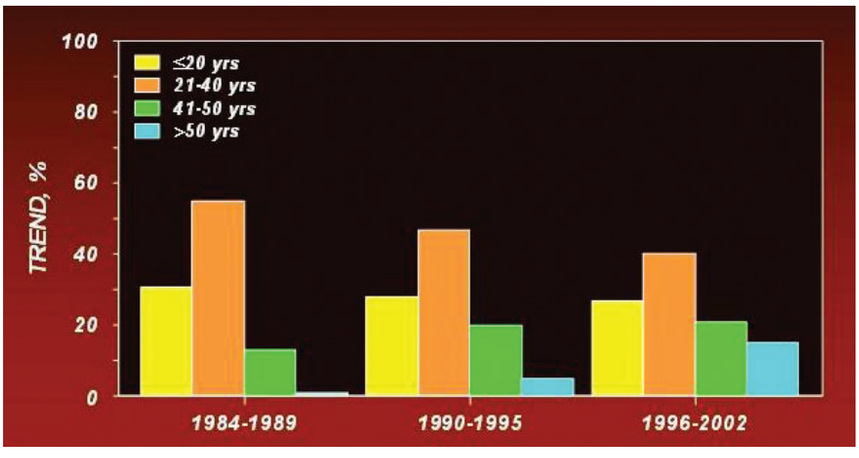
Survival

The disease state at transplant has been shown to be of primary importance in assessing risk of relapse and long term survival following transplant[7]. Data from the CIBMTR shows a significant (P=0.0001) difference between the probability of survival following transplant in those in CR1 (1st complete remission) and those in CR2[9].

Acute Myeloid Leukaemia

In the literature, the long-term survival in





Figs 4 and 5. Trends in recipient age noted over time (1984-2002). Belfast (top) compared to CIBM TR[8]

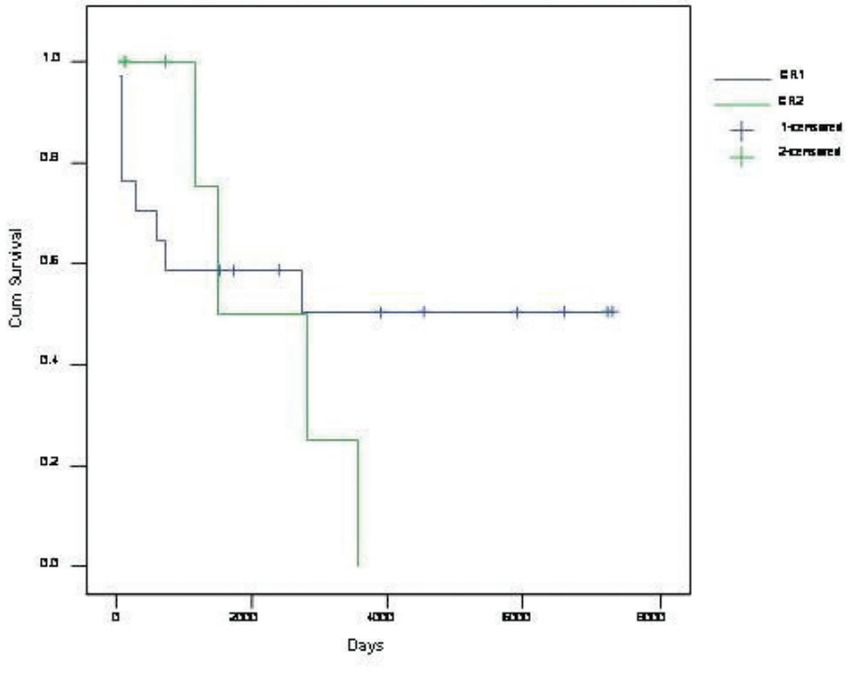


Fig 6. Survival plot of patients with AML transplanted in both CR1 and CR2

AML with chemotherapy alone has been shown to be ~40%[7]. In our group, overall survival of those patients with AML who underwent allogeneic transplant was noted to be 47%. Further evaluation revealed the survival was indeed related to disease status at transplant and these statistics were comparable with international figures (fig. 6). Those transplanted in CR1 were noted to have improved survival with an actuarial 5-year survival of 59% in CR1 compared to 33% in CR2. The CIBMTR record a 3-year survival in those patients in CR1 of 61%, while those in CR2 were noted to have a survival at three years of 48%[9]. Although three-year survival statistics were not available in our study group, due to timing of assessment forms, the results in our unit are comparable.

Acute Lymphoblastic Leukaemia

Similar differences are noted in those with Acute Lymphoblastic leukaemia (ALL). Childhood ALL has been shown to have a long-term survival of well over 75% using chemotherapy alone, however in the adult population this can be as low as 35%[11]. For this reason allogeneic transplant is an important treatment option for adults with this disease. Overall survival for this group was found to be 33%. However, actuarial 5-year survival of those transplanted in CR1 was greater at 47% compared to 31% in CR2. These results are comparable with the CIBMTR who report 3 year survival of those in CR1 of 48% with the survival in CR2 6-10% lower (Fig 7).

Chronic Myeloid Leukaemia and Aplastic Anaemia

Due to small numbers within these sub-groups, comparisons with international data were felt to be unreliable and therefore not performed.

Overall Survival

Overall mortality following transplantation in our group of patients was 55.4% with median survival at 60 months (fig. 4). In order to develop and improve the transplant procedure, it is important to determine the underlying cause of death in this group. The most common cause of death during the overall time period was disease relapse with a total of 33 patients (45%) dying from progressive disease (Fig. 8). The remaining deaths were recorded as treatment related and subdivided into GVHD, infection, interstitial pneumonitis, organ toxicity and other. As can be seen from Fig. 10 the second most common

cause of death was noted to be GVHD (22%) followed by infection (16%). CIBMTR have demonstrated similar results with death secondary to relapse at 34%, infection 17% and GVHD 15%[9].

Since the introduction of transplant, relapse and non-relapse mortality have made a significant impact on overall survival rates[12]. The majority of deaths have been found to be related to toxicity from the conditioning regime, infections, GvHD and disease relapse[12]. This has led to major progress in supportive care, immunosuppression and infection management during the transplant period[12]. During the pancytopenic phase many units (including Belfast) nurse patients in single rooms using clean air systems. The use of prophylactic anti-fungals and anti-virals is also well recognised[7]. Advances in diagnostic techniques have led to improved recognition of infective organisms, with superior broad-spectrum antibiotics enhancing survival[12].

As a result of the improving management of these patients, death from infection has reduced significantly over time[12] (fig. 9). Mortality from infection can be seen to be decreasing over time, however, the ongoing risk of death from GVHD and disease relapse remains a significant challenge to haematologists (fig. 9).

CONCLUSIONS

The data collected from patients in our unit highlights the success of transplantation in Belfast. In terms of morbidity, mortality and survival, results are comparable to those in international and European records.

Over the past 20 years advances have been made in both the transplant procedure and post transplant care leading to improvements in survival which are set to continue. With the new era of reduced intensity allografts the opportunities for those older patients previously unsuitable for transplant are encouraging.

As a successful transplant unit, we look forward to continued advances in the management of patients with life threatening haematological conditions and ever improving survival rates.

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The authors have no conflict of interest.

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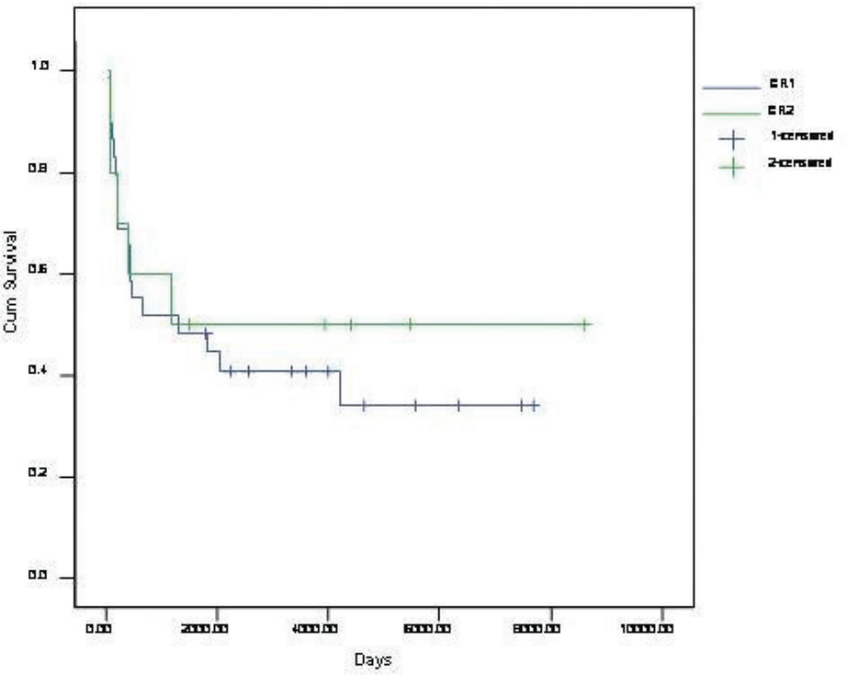

Fig 7. 10-year survival plot of those patients with ALL transplanted in Belfast in both CR1 and CR2

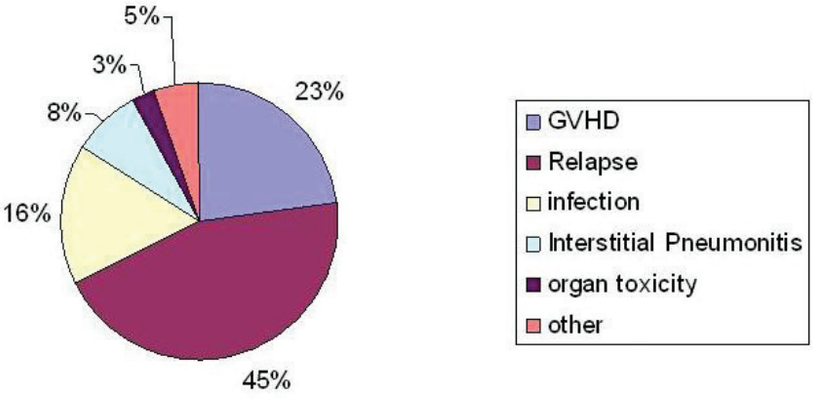

Fig 8. Cause of death following allogeneic transplant in Belfast

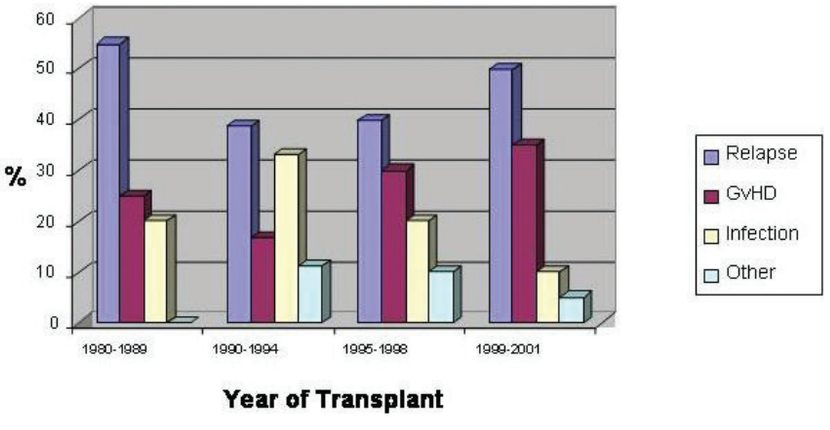

Fig 9. Cause of death following transplant in Belfast

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