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Brain Imaging and Overall Survival after Allogeneic Hematopoietic Cell Transplantation

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Authors' contributions

This work was carried out in collaboration between all authors. Authors BTC and HO designed the study, wrote the protocol and managed the data analysis. Author AD did the statistical analysis. Authors BTC, AOO and HO wrote the first draft of the manuscript and did the literature research. Authors CT and PP contributed to data collection and clinical correlation. All authors revised the manuscript and approved the final manuscript.

Research Article

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ABSTRACT

Aim: We conducted a retrospective review of all brain imaging studies in the first year after allogeneic haematopoietic cell transplantation (HCT) to determine (a) the percentage of patients with CNS neurological complications based solely on undergoing brain imaging, (b) transplant-related risk factors of undergoing brain imaging, and (c) overall survival in the patients with neurological complications compared to those transplant patients who did not have brain imaging.
Methods: Subjects were 543 consecutive recipients (August 2004-August 2007) of allogeneic HCT followed for overall survival for up to 6 years after HCT. Comparisons between patient groups with brain imaging and without brain imaging were tested using the Pearson chi-square test. Survival analyses with outcome time-to-brain-scan started

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at date of transplant and used Kaplan-Meier methods.
Results: Of 543 HCT recipients, 128 patients (24%) underwent brain imaging during the first year after transplantation. There was a greater risk of brain imaging in unrelated donor transplants and in lymphoid as opposed to myeloid malignancies (respective hazard ratios 1.45 and 1.43, *P*=0.04). Overall survival was significantly worse in unrelated donor transplants (hazard ratio 1.42, *P*=0.003) and in cord blood transplants (hazard ratio 1.68, *P*=0.02). Landmark survival analysis of patients alive 1 year after HCT showed worse survival over the next 5 years in those who had brain imaging in the first post transplant year (*P*<0.0001).
Conclusion: These results suggest that development of neurological symptoms or a sign sufficient to prompt clinicians to order brain imaging early after HCT identifies a poor prognosis in transplant population.

Keywords: Brain imaging; overall survival; allogeneic hematopoietic cell transplantation.

1. INTRODUCTION

Reported incidences of neurological complications after allogeneic hematopoietic cell transplantation (HCT) vary widely in the transplantation literature. The highest reported incidence is 46% in adult patients who underwent unrelated-donor HCT [1], and 46% in paediatric patients who had their transplants in the early years between 1976 and 1983 [2]. A more recent study of paediatric transplants reported a much lower incidence of 15.8% [3]. Most clinical studies are based on retrospective chart reviews. One prospective study of 115 consecutive transplants in the early 1990s reported neurological complications in 17% of patients in the first 3 months after transplant [4]. A difficulty in making comparisons to studies that reported lower incidences of neurological complication [5,6] may be one of definition. The clinician may have restricted the diagnosis of neurological complication to more severe CNS problems or to structurally apparent diagnoses.

Recently we reported brain imaging results in 128 consecutive transplant patients who underwent brain magnetic resonance imaging (MRI) or computed tomography (CT) imaging in the first year after HCT [7]. Indications for brain imaging in these patients included encephalopathy or confusion (40%), headache (20%), focal neurological signs (12%), seizures (10%), trauma or fall (3%), other indications (16%). In the present report, we analyze data from these patients along with consecutive HCT patients seen at the same time from the same centre who did not have brain imaging. Our purpose is to determine (a) the incidence of central nervous system (CNS) neurological complications based solely on ordering of brain imaging, (b) transplant-related risk factors that lead to brain imaging, and (c) overall survival in those patients with neurological complications compared to those patients who did not have brain imaging.

2. MATERIALS AND METHODS

Subjects were 543 consecutive recipients (August 2004-August 2007) of allogeneic HCT for haematological malignancy or a related disorder. Donors were HLA-matched siblings or unrelated. Subjects were followed for overall survival for up to 6 years after HCT through October 2010. This study was approved by our Institutional Review Board.

Comparisons between patient groups with brain imaging and without brain imaging were tested using the Pearson chi-square test for categorical data, and the two-sample t-test for continuous measurements. Tests were two-sided and the cut-off for statistical significance was 0.05. Survival analyses with outcome time-to-brain-scan started at date of transplant and used Kaplan-Meier and Cox proportional-hazards methods. Regressions were reported as models with univariate predictors, and as reduced multivariable models including just the significant predictors. Risk ratios were reported with 95% confidence intervals. Time-dependent Cox proportional-hazards model regressions with outcome of overall survival (time to death or last contact) were done along with Landmark Kaplan-Meier analysis starting at one year after transplant on all patients surviving one year.

3. RESULTS

3.1 Patient Characteristics and Risk for Brain Imaging

Patient characteristics are shown in Table 1. Recipients of allogeneic HCT (n=543) ranged in age from infancy to 75 years (median 45 years) with 56% men and 44% women. Patients were mainly non-Hispanic White (57%) or of Hispanic (29%) ethnicity. There were only slightly more sibling donors (52%, n=280) than unrelated donors (48%, n=263). Approximately the same number of patients had Non-myeloablative (48%, n=260) versus Fully ablative (52%, n=283) conditioning. The types of hematopoietic cells transplanted were peripheral blood in 437 patients (80%), bone marrow in 75 patients (14%), and cord blood in 31 patients (6%). The most common haematological diagnoses were acute myelogenous leukaemia (33%, n=178) and acute lymphoblastic leukaemia (25%, n=133). The median follow-up time of the 263 patients still alive at the date of this study was 3.55 years (range 0.37-6.02).

The results of the categorical analysis on brain imaging data are shown in Table 2. Of the 543 patients, 128 (24%) had brain imaging during the first year after HCT. A total of 173 CTs and 103 MRIs were done in these 128 patients. Median time between transplant and the first brain image was 1.33 months, with a range of 0.03 to 11.93 months. Patients who received HCT from HLA-matched unrelated donors had a marginally higher percentage of brain imaging studies (27%, 71 of 263 patients) than those who received HCT from sibling donors (20%, 57 of 280 patients). This difference was not statistically significant by categorical analysis (P=0.07). But statistical significance was shown in one predictor of the two-predictor final multivariate Cox model with a hazard ratio of 1.45 ([95% CI 1.02-2.06], P=0.04). A greater number of patients with lymphoid (27%, 72 of 265 patients) as opposed to myeloid (20%, 56 of 278 patients) malignancies had brain imaging. This difference also was not significant by categorical analysis (P=0.06) but was significant as the other predictor of the final multivariate Cox model chosen by backwards elimination (hazard ratio 1.43 [95% CI 1.01-2.03], P=0.04). The univariate hazard ratio for recipients of cord-blood HCT compared to peripheral-blood transplants was 1.81 ([95% CI 0.97-3.38], P=0.06). No effect on the likelihood of undergoing brain imaging was found in categorical analysis with other parameters, including conditioning regimen (Non-myeloablative versus Fully ablative, P=0.28), type of stem cells transplanted (bone marrow, cord blood or peripheral blood, P=0.13), or disease status at the time of HCT (P=0.21). Also, counts of CD34+ or CD3+ cells in the HCT did not affect the likelihood of undergoing brain imaging (data not shown).

Table 1. Demographics of all patients with allogeneic HCT (n=543)

Characteristic	Total Group Median (range) n (Column %)
Age at time of HCT (years)	45.2 (0.84, 74.9)
n	543
Months from HCT to First Scan	1.33 (0.03, 11.93)
n	128
Sex	
Female	241 (44%)
Male	302 (56%)
Ethnicity	
Non-Hispanic White	309 (57%)
Hispanic	157 (29%)
Asian	62 (11%)
Black	14 (3%)
American Indian	1 (0.2%)
Donor relatedness	
Sibling	280 (52%)
Matched unrelated	263 (48%)
Conditioning regimen	
Fludarabine melphalan	232 (43%)
Fludarabine (miscellaneous)	28 (5%)
Etoposide TBI	147 (27%)
Cyclophosphamide TBI	70 (13%)
Busulfan cyclophosphamide	48 (9%)
Other	18 (3%)
Stem cells transplanted	
Peripheral blood	437 (80%)
Bone marrow	75 (14%)
Cord blood	31 (6%)
Haematological diagnosis	
Acute myelogenous leukaemia	178 (33%)
Acute lymphocytic leukaemia	133 (25%)
Chronic myelogenous leukaemia	29 (5%)
Chronic lymphocytic leukaemia	7 (1%)
Non-Hodgkin's lymphoma	88 (16%)
Hodgkin's disease	16 (3%)
Myelodysplastic syndrome	53 (10%)
Multiple myeloma	21 (4%)
Myeloproliferative disease	18 (3%)

Abbreviations: HCT = Hematopoietic Cell Transplantation.

Table 2. Brain imaging data of all patients with allogeneic HCT during the first post-HCT year (n=543)

Characteristic	*Without Brain Imaging*	*With Brain Imaging*	*P-value*[a] *With vs. Without Brain Imaging*
	Total Median (Range) n (Column %)	**Total Median (Range) n (Column %)**	
Total number of patients	415 (76%)	128 (24%)	
Age at time of HCT (years)	45.2 (0.84, 74.9)	44.4 (1.6, 70.5)	0.51[b]
Donor relatedness			
Sibling	223 (54%)	57 (45%)	0.07
Matched unrelated	192 (46%)	71 (55%)	
Hematopoietic malignancy			
Lymphoid	193 (47%)	72 (56%)	0.05
Myeloid	222 (53%)	56 (44%)	
Conditioning regimen			
Non-myeloablative	172 (41%)	60 (47%)	0.28
Fully ablative	243 (59%)	68 (53%)	
Stem cells transplanted			
Bone marrow	62 (15%)	13 (10%)	0.13
Cord blood	20 (5%)	11 (9%)	
Peripheral blood	333 (80%)	104 (81%)	
Disease status at HCT			
1CR/1PR/1CP	155 (37%)	40 (31%)	0.21
More advanced disease	260 (63%)	88 (69%)	

Abbreviations: HCT = Hematopoietic cell Transplantation; 1CR = first complete remission; 1PR = first partial remission; 1CP = first chronic phase.

[a]*Pearson Chi-squared test.*

[b] *Student t-test.*

3.2 Risk of Mortality and Survival Analysis

Univariate Cox-regression analysis of overall survival in all 543 patients (Table 3) showed that the hazard of death was significantly higher in patients who had brain imaging done, with ratio 3.56 (95% CI 2.79-4.55) when treated as a time-dependent covariate (P<0.0001). Risk of death was twice as high in patients with active disease or >1 complete remission at the time of HCT (hazard ratio 1.95 [95% CI 1.50, 2.55], P<0.0001) compared to patients in first complete remission. Hazard ratios in patients undergoing HCT from matched unrelated donors were 1.42 (95% CI 1.12-1.80) compared to patients who received HCT from sibling donors (P=0.003). Hazard ratios for patients receiving cord-blood HCT were 1.68 (95% CI 1.09-2.58) compared to PBSC transplant (P=0.02). There were no significant differences in overall survival that could be attributed to age, sex, type of hematopoietic malignancy (Myeloid vs. Lymphoid), or conditioning regimen (Non-myeloablative versus fully ablative).

Table 3. Overall survival of all patients with allogeneic HCT (n=543)

Model	Univariable Cox Proportional-Hazards Model		
	n	Hazard Ratio (95% CI)	Wald-test *P*-value
Brain Imaging (time dependent covariate)	415	(baseline)	
Without Brain Imaging	128	3.56 (2.79, 4.55)	<0.0001
with Brain Imaging			
Disease status at HCT			
First remission*	195	(baseline)	
More advanced disease	348	1.95 (1.50, 2.55)	<0.0001
Donor relatedness			
Sibling	280	(baseline)	
Matched unrelated	263	1.42 (1.12, 2.80)	0.003
Stem cells transplanted			
Peripheral blood	437	(baseline)	
Bone marrow	75	0.78 (0.53, 1.13)	0.18
Cord blood	31	1.68 (1.09, 2.58)	0.02
Patient Sex			
Female	241	(baseline)	
Male	302	1.11 (0.88, 1.41)	0.37
Age at time of HCT	543	1.00 (0.99, 1.01)	0.70
Conditioning regimen			
Non-myeloablative	232	(baseline)	
Fully ablative	311	1.01 (0.80, 1.28)	0.93
Hematopoietic malignancy			
Lymphoid	265	(baseline)	
Myeloid	278	1.00 (0.79, 1.26)	1.00

**1CR/1PR/1CP: 1CR = first complete remission; 1PR = first partial remission; 1CP = first chronic phase.*

Abbreviations: HCT = Hematopoietic Cell Transplantation; CI = confidence intervals.

To determine the effect of brain imaging on overall survival in all 543 patients, we constructed a multivariate model chosen by backwards-elimination Cox. This final reduced model (P<0.0001) estimating hazard ratio of death had two predictor terms: patients who had brain imaging (treated as a time-dependent variable) having a hazard ratio of 3.59 (95% CI 2.81-4.59) over patients who did not have brain imaging (P<0.0001). Fig. 1 shows overall survival beginning year one post HCT in the 381 patients who survived the first year after transplant. Overall survival is graphed as a Landmark analysis starting one year post-transplant as there is no easy depiction of survival in the case of time-dependent variables starting at date of transplant. We take advantage of the fact that all brain imaging relevant to this study is complete by one year post-transplant, fixing the categories of comparison in advance of the start point of Landmark analysis. Survival is worse at year 2-6 in the 65 patients who had brain imaging in year 1 compared to the 316 patients who did not have brain imaging (P<0.0001).

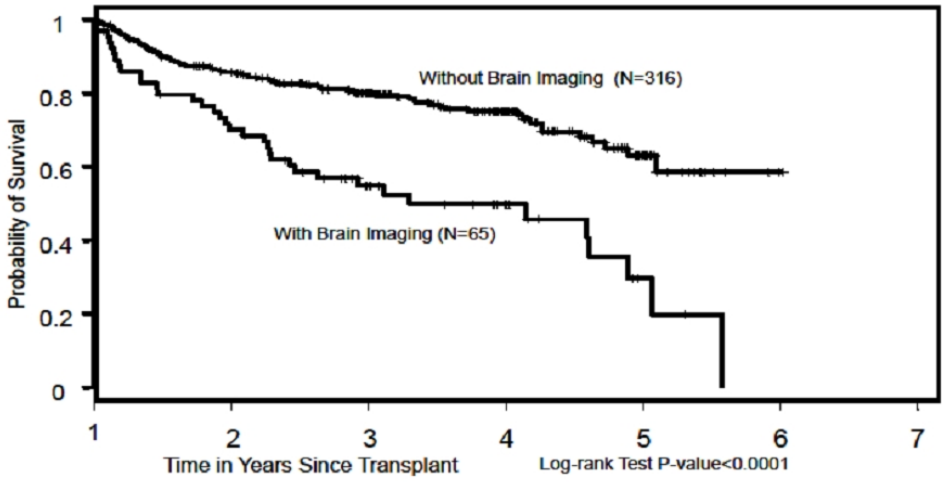

Fig. 1. Landmark Kaplan-Meier overall survival analysis starting in the second post transplant year in 381 patients who survived the first year after allogeneic haematopoietic cell transplantation (HCT)

4. DISCUSSION

We defined patients as having had a CNS complication if they underwent diagnostic brain imaging for any indication during the first year after HCT in this study. Based on this criterion, we report neurological complications in 24% of patients in the first year following HCT, an incidence similar to published results [2-6,8]. This method of determining the incidence of neurological complications eliminates selection bias in chart reviews and inconsistencies in hospital coding. However, a clear limitation is that the decision to obtain brain imaging is solely at the clinical discretion of the transplant physician. There may be practitioner-related differences between transplant centres or even at the same centre at various times. Minor CNS complications where brain imaging may be considered unnecessary would be missed and this method also fails to capture peripheral nervous system complications of transplantation. Despite these limitations, our result with the multivariate model is similar to published work reporting a higher incidence of neurological complications in unrelated-donor transplants [3].

Descriptive survival analysis in HCT studies generally use time-to-event measurements, from the date of transplant to the time of death or last contact. However, analysis of our study was complicated by the fact that brain imaging occurred at varying times after the date of transplant. To address this methodological complexity, we included time-dependent covariates in assessing the effect of brain imaging on survival. We also employed Landmark Kaplan-Meier analysis starting one year post-transplant on patients surviving one year to ensure that all relevant diagnostic brain imaging studies had been completed by the start date of descriptive survival analyses.

Consistent with the HCT literature, we found higher mortality with cord blood and unrelated-donor grafts compared to sibling-donor transplants. There was significantly higher mortality in patients with active disease or >1 relapse at the time of HCT. Nevertheless, the greatest difference in overall survival was in patients who had neurological complications. Similar higher mortality has been reported in retrospective clinical studies [4,6]. Central nervous

system (CNS) pathology such as intracranial haemorrhage, abscess, and CNS metastases were considered the major cause of death in 17% autopsy series of HCT patients [9,10]. Clearly, serious structural brain lesions contribute to the mortality of transplant patients. However, many of the neurological complications in HCT patients (approximately 50% in the more inclusive clinical series) are toxic-metabolic encephalopathy or other non-structural CNS complications [8]. Only a third of the 128 patients who had brain imaging in our study had structural abnormalities found on brain imaging (cerebrovascular complications in 10 patients, CNS infection in 9, subdural fluid collection in 6, CNS tumour recurrence in 11, and drug toxicity in 5 patients) [7]. The relatively high mortality in the group of patients without brain structural abnormality may appear unexpected, because most toxic-metabolic encephalopathy that may prompt clinicians to obtain brain imaging is not in itself life-threatening. However, as recent studies have shown, instances of severe metabolic derangement associated with encephalopathy do occur in transplant patients [11,12].

The association of early brain imaging with decreased overall survival that we report here is analogous to published studies of poor prognostic implications of pulmonary and hepatic abnormalities in HCT recipients [13,14]. Results in our patients clearly show that the clinical indication for brain imaging was itself a strong predictor of shorter survival. It is likely that by selecting patients with symptoms and signs sufficient to prompt the transplant physician to order brain imaging, we have identified patients who have evolved or are evolving a problem-laden post-HCT course with an ultimately poorer prognosis.

5. CONCLUSION

These results suggest that development of neurological symptoms or a sign sufficient to prompt clinicians to order brain imaging early after HCT identifies a poor prognosis in transplant population.

CONSENT

Not applicable.

ETHICAL APPROVAL

This retrospective study was approved by Institutional Review Board (IRB).

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COMPETING INTERESTS

The authors have no conflict of interest to disclose.

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