Allogeneic hematopoietic cell transplantation in HIV-positive patients with hematological disorders: A report from the Center for International Blood and Marrow Transplant Research (CIBMTR)

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Abstract

The role of allogeneic hematopoietic cell transplantation (alloHCT) in HIV-positive patients is not known. Using the CIBMTR database, we retrospectively evaluated 23 HIV-positive patients undergoing matched sibling (n=19) or unrelated (n=4) donor transplants between 1987 and 2003. The median age at alloHCT was 32 years. Indications for alloHCT were diverse and included malignant (n=21) and non-malignant (n=2) hematologic disorders. Nine patients (39%) were transplanted after 1996, the approximate year highly active anti-retroviral therapy became standard. The median time to neutrophil engraftment was 16 days (range 7–30) and the cumulative incidences

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of grades II – IV acute graft-versus-host disease (GVHD) at 100 days, chronic GVHD and survival at 2 years were 30% (95% C.I. 14-50), 28% (95% C.I. 12-48) and 30% (95% C.I. 14-50), respectively. At a median follow-up of 59 months, 6 patients are alive. Survival appears better among the patients transplanted after 1996: 4 of 9 patients transplanted after 1996 survive compared to 2 of 14 patients transplanted prior to 1996. These data suggest that alloHCT is feasible for selected HIV-positive patients with malignant and non-malignant disorders. Prospective studies are needed in these patients to evaluate the safety and efficacy of this modality in specific diseases.

Keywords

HIV; bone marrow transplant; malignancy; allogeneic

INTRODUCTION

Both autologous and allogeneic hematopoietic cell transplantation (HCT) are valid treatment options in patients with malignant and non-malignant hematological disorders. Among the hematologic malignancies, the incidence of non-Hodgkin's and Hodgkin's lymphoma is remarkably high in human immunodeficiency virus (HIV) positive patients [1–4] and the risk of other malignancies such as acute myeloid leukemia also appears increased [5]. Cancer is now the most common cause of death among the HIV-infected persons in the regions where highly active anti-retroviral treatment (HAART) is widely available [6].

HIV-positive patients are often excluded from consideration for HCT because of concerns about infections and other treatment-related complications. Several recent reports demonstrate the feasibility and curative potential of autologous transplantation for HIV-associated lymphomas in adults and children [7–17]. Initial reports of allogeneic hematopoietic cell transplantation (alloHCT) as a primary treatment for HIV infection failed to show the benefit of this approach either due to recurrence of HIV infection or treatment related deaths [18–20]. However, recent anecdotal reports suggest that alloHCT may be feasible and beneficial in HIV-positive patients with hematologic malignancies [21–28]. However, the role of alloHCT in these patients has not been studied in a systematic fashion.

Performing alloHCT in HIV-positive patients presents several challenges, including significant exposure to opportunistic infections prior to HCT, a high incidence of concomitant infections such as viral hepatitis, complex drug interactions between anti-retroviral and transplant-related medications, and effect of HIV on T-cells, the bone marrow environment, and the cytokine milieu. For these reasons, HIV infection might potentially impact engraftment, regimen-related toxicities, graft-versus-host disease (GVHD), infection risk, and survival.

We retrospectively evaluated 23 HIV-positive patients who underwent alloHCT between 1987 and 2003 and were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The primary objective of the study was to determine the clinical outcomes of alloHCT in HIV-positive patients. Secondary objectives were evaluation of CD4 recovery and viral loads (VL) in the post-transplant period.

PATIENTS AND METHODS

The study was conducted by the Infection and Immune Reconstitution Working Committee of the CIBMTR. Between 1987 and 2003, 50 HIV-positive patients, who underwent alloHCT have been reported to CIBMTR. After identification of eligible patients, centers were contacted for the confirmation of the HIV results. Thirty-one patients, treated at 21 centers, were confirmed to be HIV-positive. Of these, patients transplanted for primary treatment of HIV

disease (n=5) or from a syngeneic donor (n=3) were excluded. The remaining 23, who received a graft from a matched sibling (n=19) or unrelated donor (n=4) for a malignant (n=21) or non-malignant (n=2) hematologic disorder, were analyzed. Additional information regarding the history of HIV infection, opportunistic infections, anti-retroviral therapy, CD4 counts, and VL pre- and post- transplant was requested.

CIBMTR

A formal affiliation of the research division of the National Marrow Donor Program (NMDP) and the International Bone Marrow Transplant Registry at the Medical College of Wisconsin led to the establishment of the CIBMTR in 2004. The CIBMTR is a working group of more than 500 transplant centers worldwide that voluntarily contribute data on allogeneic and autologous transplant recipients to a Statistical Center at the Medical College of Wisconsin or the NMDP Coordinating Center in Minneapolis. Participating centers register and provide basic information on all consecutive transplants, and compliance is monitored by on-site audits. Detailed demographic, disease and transplant characteristics and outcome data are collected on a sample of registered patients including all unrelated donor transplantations facilitated by the NMDP in the U.S. Patients are followed longitudinally, with yearly follow-up. Computerized error checks, physician review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are done with a waiver of informed consent and in compliance with HIPAA regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

Definitions and Endpoints

Conditioning regimens were defined as myeloablative and non-myeloablative using the criteria defined by the CIBMTR [29]. At the time of alloHCT, performance status (PS) was defined according to the Karnofsky scale for patients ≥ 16 years and the Lansky scale for those <16 years of age. Primary endpoints were engraftment, acute and chronic GVHD, and overall survival. Engraftment was defined as the first of three consecutive post-transplant days that the neutrophil count was >500/mm^3. Acute GVHD events were any occurrence of grade II, III, and/or IV skin, gastrointestinal, or liver abnormalities fulfilling the Glucksberg criteria[30]. Chronic GVHD events included symptoms in any organ system fulfilling the criteria of limited or extensive chronic GVHD [31]. For analyses of survival, failure was defined as death from any cause; surviving patients were censored at the time of last follow-up.

Statistical Analysis

Probabilities of acute and chronic GVHD were calculated using cumulative incidence curves to accommodate competing risks. The competing risk for GVHD was death from any cause. Univariate probabilities of overall survival were calculated using the Kaplan-Meier estimator. Estimates of standard error for the survival function were calculated by Greenwood's formula and 95% confidence intervals (CI) were constructed using log-transformed intervals. Assessement of infections used infection density defined as the number of infectious episodes per patient days at risk, to account for multiple infections in single patients. Analyses used SAS software, version 9.1 (SAS Institute). Data were updated as of July 2007.

RESULTS

Patient and donor characteristics

Patient, HIV disease, hematologic disorder and transplant related characteristics are summarized in Table 1. Median age of recipients at alloHCT was 32 years (range, 9–43). Indications for allografting were diverse and included: non-Hodgkin lymphoma, 10; AML/

myelodysplastic syndrome, 5; acute lymphoblastic leukemia, 1; biphenotypic acute leukemia, 1; chronic myeloid leukemia, 4; aplastic anemia, 1; and inherited abnormality of erythrocyte differentiation/function, 1. The donors were: HLA-identical siblings, 19 (83%); and matched unrelated, 4 (17%). The conditioning regimens were myeloablative in 20 (87%) and non-myeloablative in 3 (13%) patients. Among the myeloablative conditioning regimens, cyclophosphamide combined with either total body irradiation (n=9) or busulfan (n=6) were the most commonly used regimens (Table 1). Most patients (16/23, 70%) received cyclosporine based GVHD prophylaxis with or without methotrexate.

Nine patients (39%) were transplanted after 1996, the approximate year HAART and VL testing became standard. For this subset of patients, the median age was 37 years (30 – 43) and disease indications for allogeneic HCT included CML (n=4), NHL (n=4) and AML (n=1). The donors were HLA-identical siblings, 6 (67%) and matched unrelated, 3 (33%). As expected, the three patients receiving non-myeloabative conditioning were transplanted after 1996.

Diagnosis and history of HIV infection

Details regarding the diagnosis and treatment history of HIV infection and infectious complications prior to transplantation were provided for 13 (57%) patients. Among these patients, the diagnosis of HIV infection was made in 4 (31%) patients prior to the diagnosis of hematologic disorder for which transplantation was performed. Five patients were diagnosed with HIV either at the time of diagnosis (n=3, 23%) or after the diagnosis (n=2, 15%) of the hematologic disorder, and 4 (31%) patients were found to be HIV-positive during alloHCT work-up. Eight of the nine patients transplanted after 1996 had detailed HIV information available. Of these, 3 patients were diagnosed with HIV prior to the onset of the disease for which the transplant was indicated. The remaining 5 patients were diagnosed with HIV concomitantly with the malignancy (n=3), between the onset of malignancy and alloHCT (n=1), or at the time of transplant work-up (n=1). The information on opportunistic infections prior to alloHCT on 13 patients is summarized in Table 1.

Anti-retroviral therapy

Information on antiretroviral therapy prior to alloHCT was available for 13 cases. For the 14 patients transplanted prior to 1996, 2 patients were not on anti-retroviral therapy before or during transplantation and 4 patients received either monotherapy with zidovudine (n = 1) or didanosine (n=2) or double therapy (n=1) with didanosine and stavudine. Data was not available on the remaining 8 patients transplanted prior to 1996. Among the 9 patients transplanted after 1996, data on anti-retroviral therapy were available for 7. All but one patient was on triple therapy. Information was provided that 2 patients had planned cessation of their antiretroviral therapy peri-transplant and the therapy was restarted within 1-month post-HCT.

Outcomes of alloHCT in HIV-positive patients

The outcomes of HIV positive patients undergoing alloHCT are summarized in Table 2.

Engraftment—Of the 23 patients, 18 achieved neutrophils engraftment at a median of 16 days (range 7–30). Three of the five patients who did not achieve engraftment had very early deaths (on days 2, 6 and 10) due to regimen-related toxicities. One patient treated with non-myeloablative conditioning and an HLA-matched unrelated donor bone marrow transplant had secondary graft failure.

Graft-versus-host disease—Of the 23 patients, five developed grade II, two developed grade III, and one developed grade IV acute GVHD. The cumulative incidence of acute GVHD (grade II-IV) was 30% (95% CI 14 – 50) at 100 days (Fig 1A). Median onset of acute GVHD

was 16 (range, 5 – 47) days after alloHCT. The cumulative incidence of chronic GVHD at 2 years was 28% (95% CI, 12 – 48) (Fig 1B).

Survival—The median follow up of surviving patients (n=6) was 59 (range, 23–90) months. Kaplan-Meier probabilities of survival at 100-days, 1 and 2-years were 57% (95% CI 36-76), 30% (95% CI 14-50), and 30% (95% CI 14-50), respectively (Fig 2). Four of 9 patients transplanted after 1996 survive compared to 2 of 14 transplanted prior to 1996. Primary causes of death are summarized in Table 2. Of particular note, among the 12 patients receiving high-dose TBI containing conditioning regimens, there were 6 deaths due to pulmonary toxicity.

Post-transplant infections—Detailed data on infections in the post transplant period were available for 19 patients and summarized in Table 2. Culture positive bacterial infections and CMV reactivation were the two most common infection related events. The infection density for the entire cohort was 1.16 infections per patient in the first 100 days. When analyzed for patients prior to 1996 and after 1996, the infection densities were 0.95 and 1.43 infections per patient in the first 100 days, respectively.

CD4 counts and VL—Information on CD4 counts was available for 9 patients, and 7 had data available on both pre- and post-transplant counts. Among 8 patients with available pre-transplant CD4 counts, the median CD4 count was 173/μL (0 – 1200) at a median of 24 (11–65) days before transplant. At 1-month post HCT, the median CD4 count was 38/μL (0 – 370). At 1 year after HCT, CD4 counts in the 3 patients measured were 640, 302, and 503/μL respectively.

VL data were submitted for 6 patients, although pre- and post-transplant values were only available on 4 patients. Pre-HCT, 4 patients had no detectable virus; the remaining patient had 3.6 log copies. At a median of 58 (28 – 104) days after HCT, the median VL was 1.7 log copies (range, undetectable – 4.4 log copies) in the 5 patients with available data. At 1-year post HCT the VL in the 3 patients checked were 1.7, 3.0, and 4.4 log copies respectively.

DISCUSSION

This is the largest series assessing the outcome of alloHCT among HIV-positive patients. Primary engraftment was achieved in most of the evaluable patients and one patient undergoing non-myeloablative transplant had secondary graft failure. This engraftment pattern seems comparable to HIV-negative patients. Cumulative incidences of acute and chronic GVHD do not appear much different than would be expected from HIV-negative patients.

Survival was low in this series, particularly among patients transplanted prior to 1996. Major causes of death were regimen-related toxicities and infections. Among the regimen-related toxicities, pulmonary toxicity was common, particularly among patients receiving high-dose TBI. A high incidence of pulmonary toxicity may be related to opportunistic infections prior to alloHCT. Data on pre-transplant opportunistic infections were available in 57% patients. Due to limited sample size, the impact of opportunistic infections on post-transplant outcomes could not be assessed. With modern supportive care strategies, and conditioning regimens with lower toxicity, regimen-related toxicities may be reduced. Infectious complications were the other main cause of death and the risk of post-transplant infections may be higher in these patients compared to HIV-negative patients although it does not seem so in our cohort in which patients had just over 1 infection in the first hundred days following transplant. Information about CD4 counts and VL in the post-transplant period was available for few patients. There was a decrease in CD4 counts between pre-transplant and 1 month post- transplant and subsequent slow recovery to >300/μL at 1 year in three patients for whom these data were available. The recovery does not appear to be slower in the HIV-positive compared to HIV

negative patients, as in HIV-negative marrow recipients, CD4 counts typically recover to >200/ml by 1-year [32].

Our report is limited by small number of patients treated in the post HAART era and incomplete information on CD4 counts and VL. Nevertheless, the survival of patients treated after 1996 appears better compared to patients treated before 1996. This is presumably due to the effect of better supportive care strategies and the routine use of HAART, which became standard around this time. This report demonstrates that some patients treated for various malignant and non-malignant hematologic disorders achieved long-term disease control. Due to heterogeneous study population, it is difficult to draw conclusions about the efficacy of this treatment modality for a particular disease. With the availability of HAART, there appears to be an increasing trend to use autologous transplantation in HIV-positive patients with lymphoma although these patients still rarely undergo alloHCT. This may be related to the hesitancy of physicians to use this modality due to concerns about high treatment related mortality and lack of published data. There are increasing data in solid organ transplantation that the outcomes of transplantation in HIV-positive patients are not inferior to HIV-negative patients [33,34]. Using the kidney transplant data of United Network for Organ sharing, a recent study showed that graft and patient survival of 38 HIV-positive patients were comparable to HIV-negative patients [34]. Therefore, there is increasing debate about the ethical justifications of excluding HIV positive patients for transplantation and cancer clinical trials [35]. Many researchers are of the opinion that the situation of a well-controlled HIV infection is not any different from medical co-morbidities requiring regular treatment.

In summary, our data show that despite early toxicity due to conditioning regimens and the risk of opportunistic infections, several patients achieved prolonged survival. Given the improvements in supportive care, availability of conditioning regimens with lower toxicity and the ability to suppress HIV VL with currently available medical care, alloHCT should not be dismissed as a treatment option in HIV-positive patients with hematologic disorders for whom alloHCT is considered the therapy of choice. Prospective studies are needed in HIV-positive patients to evaluate the efficacy of this modality in specific diseases and determine optimal transplantation and antiretroviral strategies.

Acknowledgments

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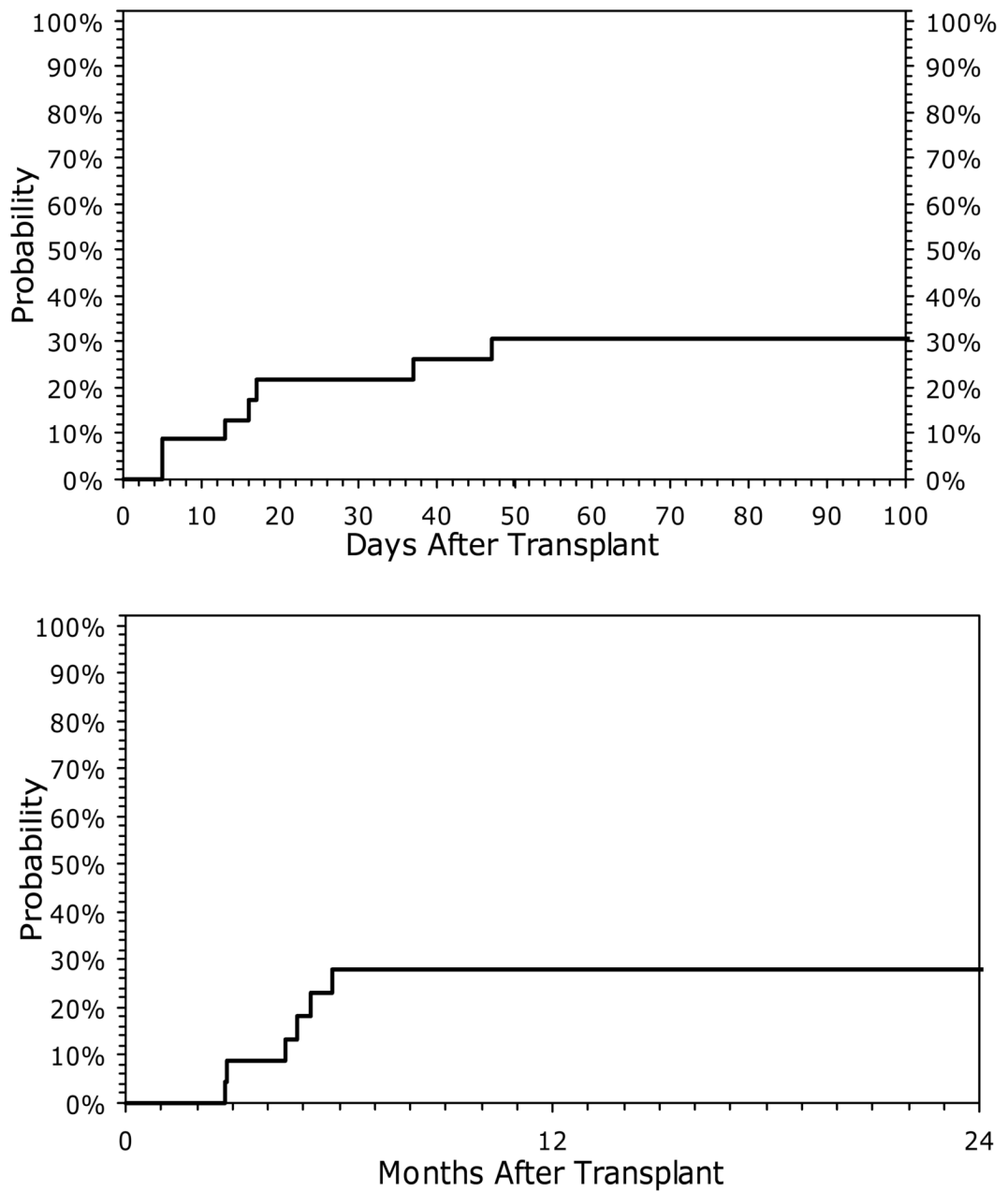
Figure 1.
Cumulative incidence of acute (A) and chronic (B) graft versus host disease in 23 patients with HIV receiving allogeneic HCT
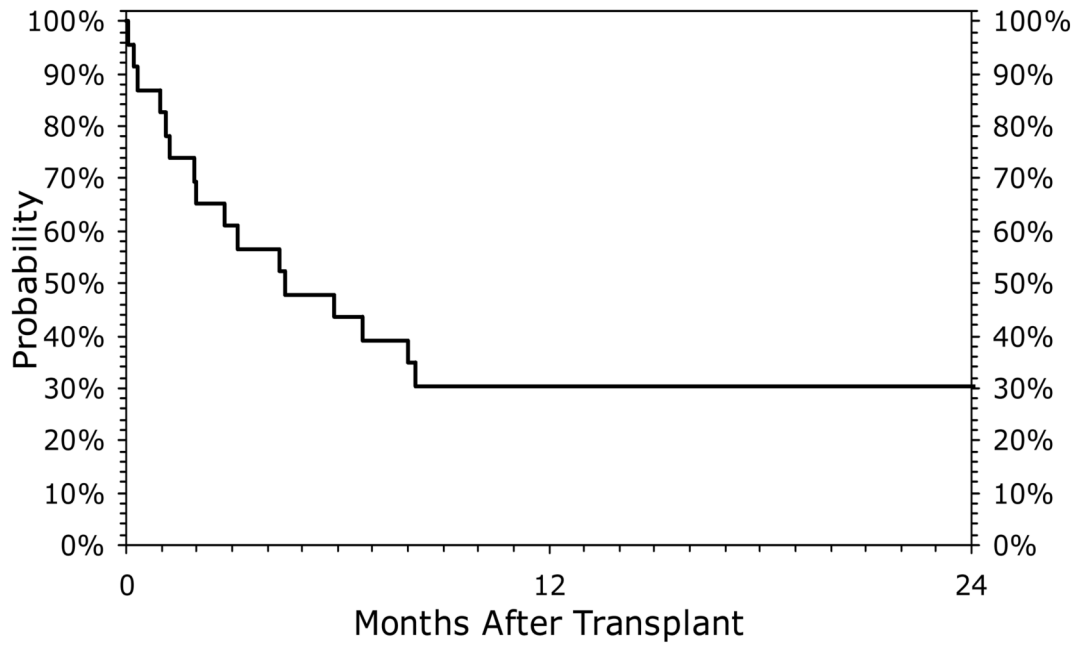
Figure 2.
Overall survival of 23 HIV positive patients undergoing allogeneic transplant for hematologic disorders

Table 1

Patient, disease and transplant related characteristics

Characteristics	N eval	N
Number of patients	23	23
Number of centers		17
Median age at alloHCT, (range), years	23	32 (9–43)
Age at HCT, years	23	
≤20		3 (13%)
21–40		17 (74%)
>40		3 (13%)
Gender, male	23	18 (78%)
Performance status at alloHCT	23	
≤80		7 (30%)
>80		16 (70%)
Patients with detailed HIV data	23	13 (57%)
Co-infection with hepatitis virus at alloHCT	10	
HbsAg positive		1 (10%)
HCV antibody positive		1 (10%)
Timing of diagnosis of HIV infection	13	
Prior to diagnosis of disorder for alloHCT		4 (31%)
At the time of diagnosis of disorder for alloHCT		3 (23%)
After diagnosis of disorder of alloHCT		2 (15%)
Incidental detection during alloHCT work-up		4 (31%)
Opportunistic infections prior to alloHCT	13	
PCP		2 (15%)
CMV		4 (31%)
Invasive Fungal		1 (8%)
Mycobacteria		1 (8%)
Others		1 (8%)
Anti-retroviral therapy prior to alloHCT	13	
Patients transplanted before 1996	6	
None		2 (33%)
Monotherapy		3 (50%)
Double therapy		1 (17%)
Patients transplanted after 1996	7	
None		0 (.)
Mono or double therapy		1 (14%)

Characteristics	N eval	N
Triple therapy		6 (86%)
Indication for alloHCT	23	
Malignant		
NHL		10 (43%)
Low grade		1
Intermediate		4
High-grade		5
Acute Leukemia		7 (30%)
MDS/AML		5
ALL		1
Biphenotypic AL		1
CML		4 (17%)
Non-malignant		2(9%)
Aplastic anemia		1
Inherited erythrocyte disorder		1
Interval from diagnosis of blood disorder to alloHCT, median (range), months	23	10 (4–172)
Year of alloHCT	23	
1987–1995		14 (61%)
1996–2003		9 (39%)
Graft type	23	
BM		18 (78%)
PB		5 (22%)
Donor type	23	
HLA-identical sibling		19 (83%)
Matched unrelated		4 (17%)
Recipient/Donor CMV status	23	
+/+ or +/− or −/+		19 (83%)
−/−		2 (9%)
Unknown		2 (9%)
Conditioning regimens	23	
Myeloablative		
CY+TBI+/−others		9 (39%)
TBI+/− others		3 (13%)
Bu+CY+/−others		6 (26%)
CY+/−others		2 (9%)
Non-myeloablative		3 (13%)
GVHD prophylaxis	23	

Characteristics	N eval	N
CSA/FK-506+/− MTX		16 (70%)
MTX+/−others		3 (13%)
T-cell depletion		1 (4%)
Others		3 (13%)

alloHCT, allogeneic hematopoietic cell transplant; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus; PCP, pneumocystis carinii pneumonia; CMV, cytomegalovirus; NHL, non-hodgkin's lymphoma; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; BAL, biphenotypic acute leukemia; CML, chronic myeloid leukemia; BM, bone marrow; PB, peripheral blood; CY, high-dose cyclophosphamide; TBI, total body irradiation; Bu, busulphan; GVHD, graft-versus-host disease; CSA, cyclosporine; FK-506, tacrolimus; MTX, methotrexate

Table 2

Outcomes in HIV-positive patients undergoing alloHCT for malignant and non-malignant hematological disorders

Outcomes	N eval	N
Median days to neutrophil engraftment, (range)	18	16 (7–30)
Cumulative incidence of Grade II-IV acute GVHD, Prob. (95% C.I.)	23	
@ 100 days		30 (14–50)%
Cumulative incidence of chronic GVHD, Prob. (95% C.I.)	23	
@ 1 year		28 (12–48)%
@ 2 years		28 (12–48)%
Episodes of infection post HCT		
≤100 days		
Culture positive bacterial		10
Invasive fungal		1
PCP		0
CMV reactivation		3
Mycobacteria		0
Hepatitis B or C		1
Others		5
>100 days		
Culture positive bacterial		4
Invasive fungal		1
PCP		0
CMV reactivation		0
Mycobacteria		0
Hepatitis B or C		1
Others		2
Median follow-up of survivors, (range), months	6	
Prior to 1996 (n=2)		75 (59–90)
After 1996 (n=4)		51 (23–74)
Overall survival, Prob. (95% C.I.)	23	
@ 1-y ear		30 (14–50)%
@ 2-years		30 (14–50)%
Primary causes of death	17	
Disease relapse		1 (6%)
NRM		
Regimen-related toxicities		
Pulmonary toxicity		6 (35%)
Other organ toxicities		3 (19%)

Outcomes	N eval	N
Graft failure		1 (6%)
Infections		4 (24%)
GVHD		1 (6%)
Others		1 (6%)

GVHD, graft-versus-host disease; PCP, pnemocystis carinii pneumonia; CMV, cytomegalovirus; NRM, non-relapse mortality