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Clinical characteristic and outcome of HHV-6 encephalitis after allogeneic hematopoietic cell transplantation: A study of Infectious Disease Working Party of EBMT

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Author contributions

KNW designed the study and revised critically the manuscript. NK collected the data. GT performed the statistical analysis. KP and SC analysed the data and wrote the paper. RZ, GNF, AS, HE, MGV, JMFN, NC, MC, RM, MG, HS, JP, JS, AN, AK, MG, NK, MJPG, MY, TG, CR, AC, MLD, AAA, MIR, MM, JS, RDLC, PL, DA, collected and reported the data to the EBMT Registry and revised critically the manuscript. PL, JS, DA, RDLC revised critically the manuscript. All authors approved the final version of the manuscript.

Data Availability' statement

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request after approval of the scientific board of the Infectious Diseases Working Party of EBMT.

Disclosures

This is a Registry study conducted under the scientific supervision of IDWP-EBMT. All authors have no conflict of interest concerning this study to disclose.

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Abstract

Human herpes virus-6 (HHV-6) is the main cause of viral encephalitis in patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT). From January 2005 to December 2014, 97 patients with HHV-6 encephalitis were reported in the EBMT registry. The incidence was 0.45% after the first allo-HCT and varied with the type of donor and of stem cell source: sibling donor 0.06%, unrelated donor 0.68%, haploidentical donor 0.51%, cord blood 2.14%, bone marrow 0.20%, peripheral blood 0.44%. HHV-6 encephalitis occurred at a median time of 31 days from allo-HCT (range 16–317 days). With a median follow-up of 5.28 years, the 5-yr OS was 24.7%. The causes of death were: disease relapse/progression 11, infection 23, non-infectious cause 33, not specified 5. Forty-four deaths (61.1%) occurred within 90 days from diagnosis of HHV-6 encephalitis and in 24 HHV-6 encephalitis was considered a contributory cause. Eight-seven patients received treatment mainly with foscarnet or ganciclovir. In multivariate analysis, bone marrow/peripheral blood stem cell source and nonmyeloablative conditioning regimen were significant factors for lower survival.

In conclusion, the incidence of HHV-6 encephalitis was low but associated with high mortality irrespective of antiviral treatment. This confirms the need for further research in this setting.

Introduction

Human herpesvirus (HHV)-6 infection is reported in 30-70% of allogeneic hematopoietic cell transplantation (allo-HCT) recipients[1–4]. Although two distinct species of HHV-6 are known, HHV-6A and HHV-6B, only HHV-6B infection is associated with several human organ diseases. Nevertheless, encephalitis is the only end-organ disease where the pathogenicity of HHV-6B is proven[5–7]. HHV-6 infection is reported as the most frequent cause of encephalitis after allogeneic HCT[8,9], with an incidence ranging between 0.5% to 11.6% [4,7], and an attributable mortality of 12.9% after 100 days from diagnosis[6]. The main risk factors for HHV-6 encephalitis are cord blood transplantation (CB), acute grade II-IV graft versus host disease (GVHD), mismatched unrelated donors (MUD), and engraftment syndrome[3–5,8,10]. More recently, an unexpectedly higher incidence of HHV-6 encephalitis has been reported in haploidentical allo-HCT performed with some platforms of *ex-vivo* T-cell depletion characterized by a graft inoculum rich in CD4+ T-cells, which are the natural reservoir of the virus [11,12].

In this retrospective study, the clinical characteristics and outcome of HHV-6 encephalitis in patients receiving allo-HCT in centers belonging to the European Society for Blood and Marrow Transplantation (EBMT) were analysed.

Patients and Methods

The study was approved by the scientific board of the Infectious Disease Working Party (IDWP) of EBMT and included allo-HCT patients, transplanted from January 2005 to December 2014, who matched the definition of HHV-6 encephalitis (see definitions). The general demographic, clinical, and transplant data of the case patients were extracted from the EBMT registry while additional information on HHV-6 infection and disease was collected using a dedicated case report form.

Informed consent was obtained from all participants of EBMT Registry. Patient data collection was performed according to the European regulation for general data protection.

Definitions

For this study, HHV-6 encephalitis was defined by the presence of all the following three criteria: (1) clinical signs or symptoms of central nervous system (CNS) dysfunction consistent with encephalitis; (2) detection by PCR of HHV-6 DNA in cerebral spinal fluid (CSF); and (3) absence of other identified causes of CNS dysfunction, including other infectious agents[5,6]. The time of encephalitis diagnosis was defined as the date of HHV-6 DNA detection in CSF. CNS dysfunction was described as: disorientation in time and place, loss of consciousness, change of personality, behaviour changes, convulsions, memory loss, or dysesthesia not attributable to peripheral neuropathy[13,14]. Considering that magnetic resonance imaging (MRI) has been described as normal in up to 30% of patients[13,15,16], and the lack of a common diagnostic protocol among participating centers [17], it was not a part of the inclusion criteria.

The contribution of HHV-6 encephalitis in determining the cause of death was based on the clinical judgment of the local investigator.

HHV-6 infection was defined as a PCR DNAemia > 1000 copies/mL on plasma or blood[5]. Surveillance, monitoring, or diagnostic assessment of other DNA-virus infections such as cytomegalovirus (CMV), adenovirus (ADV), and Epstein-Barr virus (EBV) by blood or plasma PCR followed the center policies, according to the type of transplant and the risk characteristics of patients.

Statistical analyses

Descriptive results were reported by using absolute and percentage frequencies for categorical variables, whilst median and range were used for continuous variables. The overall survival was performed by using the Kaplan-Meier methods, and compared by using the log-rank test. The univariate and multivariate analysis was performed by using the Cox regression model. Variables with a p <0.1 in the univariate analysis entered the multivariate model. A p <0.05 was considered statistically significant.

174

175 **Results**

176 During the study period, 100 patients with HHV-6 encephalitis were reported by the 41 EBMT
177 participating centers. The number of allo-HCTs performed in the same period by the centers that
178 reported cases of HHV-6 encephalitis was 22,492 in 20,148 patients.

179 Three of 100 patients did not meet all the study inclusion criteria because no lumbar puncture was
180 performed: two patients had a neurological picture consistent with encephalitis (one had altered
181 consciousness/confusion and abnormal MRI; one had short term memory loss, altered
182 consciousness and seizures but normal MRI) and HHV-6 DNAemia (viral load of 2.5×10^6 copy/ml
183 in one patient, while the viral load was not reported in the second one); the third patient had a
184 clinical picture of encephalitis (short-term memory loss, altered consciousness, seizures) with MRI
185 imaging consistent with limbic encephalitis while the search of HHV-6 in the blood was not
186 performed. These 3 patients were excluded from the analysis.

187 Demographic, underlying disease, and transplant characteristics of the 97 case patients are shown in
188 Table 1. Sixty-eight percent of patients were male, and 21% were younger than 18 years. The donor
189 type was mainly an unrelated donor (91%), while the source of hematopoietic stem cells was bone
190 marrow (BM) in 11%, peripheral blood (PB) in 67% and CB in 22% of all HCTs. CB was used in
191 45% (9/20) of HCT performed in patients $\leq$ 18 years while BM/PB was used in 84% (65/77) of
192 HCT performed in patients > 18 years (table 1S). The source of stem cell was Myeloablative and
193 nonmyeloablative conditioning regimens were used in 57% and 41% of allo-HCTs, respectively,
194 while it was unknown in 2%. The use of myeloablative conditioning regimen was significantly
195 associated with age: 95% (19/20) in patients < 18 years versus (vs.) 48% (36/75) in patients $\geq$ 18
196 years, $p < 0.001$ (table 2S).

197 Ninety-two cases of 97 HHV-6 encephalitis occurred (97%) after the first allo-HCT. The frequency
198 of HHV-6 encephalitis was 0.45% (92/20418) among the first allo-HCT and 0.24% (5/2074) in the

group of two or more allo-HCTs. Considering the cases of HHV-6 encephalitis after a first allo-HCT, the frequency varied according to the type of donor and the stem cell source: sibling donor 0.06% (4/6918), unrelated donor 0.68% (83/12191), haploidentical donor 0.51% (5/981), p <0.001, and CB 2.14% (20/936), BM 0.20% (10/5088), PB 0.44% (62/14192), $p < 0.001$.

Characteristics of HHV-6 encephalitis

All 97 patients presented neurological signs and symptoms consistent with the clinical diagnosis of encephalitis while 65 patients were also febrile and 32 patients had skin rash. HHV-6 was detected on the cerebrospinal fluid by qualitative PCR in 51 patients (53%) and by a quantitative PCR in 46 patients (47%), the median viral load being 7615 copies/ml, range 215– 18000000.

The search of HHV-6 DNA on blood/plasma/serum was performed in 63 of 97 patients (65%) and resulted positive in 51 patients (81%): 18 patients were tested by qualitative PCR while 33 patients were tested by a quantitative PCR, with a median number of copies/ml of 15630, range 200-4458500.

Radiological investigation was performed with computed tomography (CT) scan and MRI in 69 and 81 patients, respectively and abnormalities were reported in 12 cases (17.4%) with CT scans and in 51 cases (63%) with MRI.

HHV-6 encephalitis occurred at a median time of 31 days from allo-HCT (range: 16–317 days) without significant differences according to the age group: 27 days (range: 19-225) for age $\leq$ 18 years, 31 days (range: 19-317) for age 19-49 years, and 33 days (range: 16-203) for age $\geq$ 50 years; or according the stem cell source: 37 days (range: 19-225) for CB recipients and 30 days (range: 16-317) for BM or PB recipients.

Outcome

The 28-day, 90-day and 1-year OS were 77% (95% C.I. 69- 86), 55% (95% C.I. 46- 66), and 41% (95% C.I. 32-52), respectively (Figure 1). With a median follow-up of 5.28 years (95% confidence interval (CI), 5.01-7.83) the 5-yr OS was 24.7% (95% C.I.,17.1-35.6) while 72 of 97 (74.2%)

patients died (table 1). Five of 25 patients alive at the follow-up were reported to have sequelae related to previous HHV-6 episodes although a detailed description of the type and the severity of sequelae was not available. According to the local investigator's judgment, the main cause of death was: relapse or progression of the underlying disease 11 (15.3%), infection cause (any) 23 (31.9%), non-infectious cause 33 (45.8%) that was GVHD in 24 of 33 (72.7%), while it was not specified in 5 (6.9%). Forty-four of 72 deaths (61.1%) occurred 90 days after diagnosis of HHV-6 encephalitis. In 24 of 44 90-day deaths (54.5%) the local investigator defined HHV-6 encephalitis as a contributory cause of death because it was clinically present at death in 2 of 5 relapsed patients, in 14 of 18 patients who died from any infection cause, and in 8 of 19 patients who died from a non-infectious cause.

In univariate analysis, the factors associated with lower OS after HHV-6 encephalitis were the type of stem cell source and intensity of conditioning regimen: BM/PB graft 34% (95% CI, 25%-47%) vs. CB 67% (95% CI, 49%, 90%), HR 2.26 p=0.01; and nonmyeloablative conditioning regimen 28% (95% CI, 17%-45%) vs. myeloablative conditioning regimen, 51% (95% CI, 39%-66%) HR 1.82, p=0.01 (table 2). Stem cell source and intensity of conditioning regimen were confirmed in the multivariate analysis as significant factors for overall mortality: BM/PB vs. CB HR 2.21 (95% C.I., 1.12-4.35), p=0.02; nonmyeloablative conditioning vs. myeloablative conditioning HR 1.76 (95% C.I. 1.09-2.83), p= 0.02.

Eighty-seven of 97 patients (89.7%) received an antiviral treatment for HHV-6 encephalitis, as follows: foscarnet monotherapy, 32 patients for a median of 19 days, range 1-111 days; ganciclovir monotherapy, 29 patients for a median of 22 days, range 7-121; ganciclovir followed by foscarnet, 17 patients for a median of 29 days, range 12-75; combination of ganciclovir and foscarnet, 7 patients for a median of 15 days, range 7-38; cidofovir, 2 patients for 4 weeks.

Ninety-day mortality after the diagnosis of HHV-6 encephalitis was 56% (18/32) in patients treated with foscarnet, 38% (11/29) in patients treated with ganciclovir, 42% (10/24) in patients treated

with the combination of the sequence of ganciclovir plus foscarnet, (10), while the two patients treated with cidofovir were alive. In the group of 10 untreated patients, 5 deaths occurred by 90 days and 3 deaths occurred thereafter.

Discussion

This study represents an attempt to assess the incidence and the outcome of HHV-6 encephalitis in centers belonging to the EBMT network. Overall, HHV-6 encephalitis was a rare complication with an incidence of 0.45% over a 10-year period.

We recognize that this figure is lower than that reported by other authors. Considering that the reporting of infectious complications in the EBMT registry was performed voluntarily and the difficulty in defining the cause of CNS acute disease in allo-HCT patients, we can hypothesize that this incidence is underestimated. In a prospective study performed by the IDWP collecting CNS clinical events over two years (2000-2002), the infectious events were nearly half of the non-infectious events, which were mainly vascular events, and among 58 infectious complications, only two were attributed to HHV-6 CNS infection [18]. Nowadays, the more extended use than one decade ago earlier of PCR assays for CSF analysis and MRI imaging allows an improvement in defining the causes of CNS acute dysfunction. We excluded from our analysis three patients who did not perform the lumbar puncture to confirm the clinical suspicion of HHV-6 encephalitis although the presence of clinical signs and symptoms of encephalitis, together with HHV-6 detection in blood or radiological evidence of limbic encephalopathy, has been accepted to define HHV-6-associated encephalitis[14].

Recently, in a retrospective study in the adult Japanese population the incidence of HHV-6 encephalitis was 3.6% and associated with the use of CB as a stem cell source, the adoption of antiviral prophylaxis different from letermovir and the occurrence of GVHD that needed treatment

with steroids[19]. The use of CB was associated with a higher incidence of HHV-6 encephalitis also in this study.

HHV-6 encephalitis occurred early after HCT irrespective of the age of the recipient (pediatric vs. adult) and the stem cell source. This is in line with other reports where HHV-6 encephalitis was observed most commonly within 4-6 weeks after transplant [19,20].

In the survival analysis, adult age, bone marrow or peripheral blood stem cell source, and non-myeloablative conditioning regimen were associated with lower survival after HHV-6 encephalitis. In this study, these factors defined a high-risk patient profile for overall mortality. Our explanation of these results is that adult transplant recipients have a lower survival probability than pediatric recipients either for the more frequent presence of comorbidities, requiring a HCT with a nonmyeloablative conditioning, and for the biology of underlying malignant diseases in adults that have a higher relapse risk than the pediatric malignant diseases. We think that the reason why CB grafts had a better survival outcome was that this procedure was adopted in more than half of cases in children and young adults affected by acute lymphoblastic leukemia who had a better transplant outcome than adults transplanted with a BM or PB stem cell source.

No drug is officially approved to treat HHV-6 infection or disease. While the treatment of asymptomatic post-transplant HHV-6 DNAemia is not recommended, antiviral treatment of HHV-6 encephalitis with foscarnet or ganciclovir is recommended by guidelines[5,21]. Foscarnet and ganciclovir are considered first-line treatments, and the choice is based on the clinician's assessment of the patient's comorbidities, the risk for side effects, and drug-drug interactions. In this study, the type of antiviral treatment was not associated with significant differences in early mortality. Accordingly, no significant difference in efficacy has been reported between foscarnet and ganciclovir monotherapy. A better response rate and a lower sequelae rate after HHV-6 encephalitis have been reported for both antivirals when used at a full dose (foscarnet $\geq$ 180 mg/kg, ganciclovir $\geq$ 10 mg/kg), but these did not lead to differences in terms of 30 days and 100 days overall survival

after HHV-6 encephalitis[6]. Cidofovir, though effective *in vitro* against HHV-6, has limited data on efficacy and can be considered an option as rescue or an alternative after treatment with foscarnet or ganciclovir[5,22,23]. Brincidofovir, a prodrug of cidofovir, might be an option in the future but currently is not available [24].

In conclusion, in this retrospective study, the incidence of HHV-6 encephalitis was low, but high mortality was confirmed irrespective of antiviral treatment. The risk factors associated with higher mortality and lower OS were adult age, the use of BM or PB as a stem cell source, and the nonmyeloablative condition regimen. Even though this study refers to patients transplanted more than a decade ago, it describes a very large series of post-allo-HCT HHV-6-related encephalitis and confirms the role of HHV-6 in the occurrence of encephalitis complications. Future research is needed to assess is usefulness of HHV-6 DNAemia monitoring, the correlation of HHV-6 infection with the development of HHV-6-related organ diseases, and the role of pre-emptive antiviral treatment in preventing HHV-6 encephalitis.

Author Contributions

Annex 1.

List of EBMT center identification code (CIC), principal investigator, city and state, of participating centers.

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Figure 1. Probability of overall survival at 28 days, 90 days and one year of the patients with HHV-6 encephalitis

	28 days	90 days	1 year
Events	22	44	57
OS probability	77% (95% C.I., 69- 86)	55% (95% C.I., 46-66)	41% (95% C.I., 33-52)

Table 1. Demographic and transplant characteristics of patients with HHV-6 encephalitis

Legend.

HHV-6, Human Herpes Virus-6 encephalitis; M, male; F, female; Allo-HCT: allogeneic hematopoietic cell transplant; N.S.: not specified; CT, computed tomography; MRI, magnetic resonance imaging; CMV, cytomegalovirus; ADV, adenovirus; BKPyV, BK polyoma virus; HHV-7, human herpes virus-7; OS, overall survival; C.I., confidence interval

Table 2. Univariate analysis of risk factors for overall survival in patients with HHV-6 encephalitis

Legend.

M, male; F, female; Allo-HCT, allogeneic hematopoietic cell transplantation; CB, cord blood; BM, bone marrow; PB, peripheral blood; Haplo, haploidentical

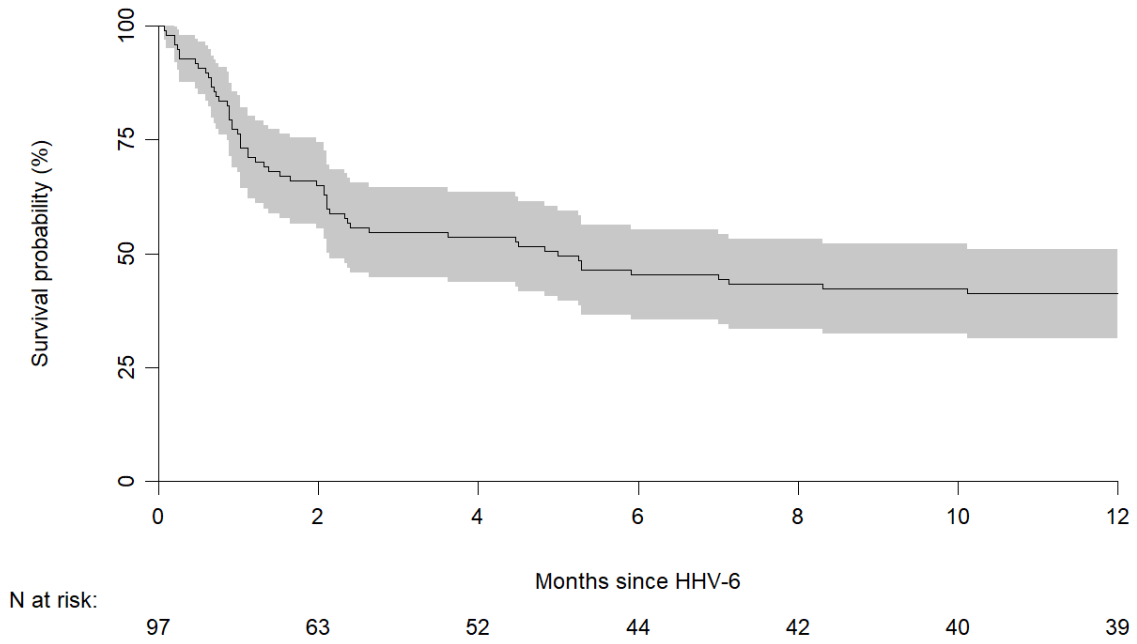
Survival probability (%)
100
75
50
25
0
0
2
4
6
8
10
12
Months since HHV-6
N at risk:
97
63
52
44
42
40
39

Table 1. Demographic and transplant characteristics of patients with HHV-6 encephalitis

Number of HHV-6 encephalitis episodes	97
Age at allo-HCT, median (range)	48.4 (0.4-77.5)
≤ 18 year >18 year	20 (21%) 77 (79%)
M/F	66/31
Underlying disease Acute leukaemia, Myelodysplastic/Myeloproliferative disease Chronic leukaemia, Lymphoma Hodgkin/Non-Hodgkin Plasma cell disorders Bone marrow failure Inherited disorders	 44 (45%) 24 (25%) 10 (10%) 8 (8%) 6 (6%) 2 (2%) 3 (3%)
Donor type Sibling Unrelated donor Haploidentical donor	 4 (4%) 88 (91%) 5 (5%)
Conditioning regimen Myeloablative Non-myeloablative Not specified	 55 (57%) 40 (41%) 2 (2%)
Stem cell source Bone marrow Peripheral blood Cord blood	 11 (11%) 65 (67%) 21 (22%)
1st allo-HCT/≥ 2nd allo-HCT	92/5
Interval allo-HCT-HHV-6 encephalitis median, range	 31 days, 16 days – 317 days
Neurological symptoms Short term memory loss Altered consciousness, encephalopathy, confusion, Seizures	 51/94 (54.3%), N.S. in 3 89/96 (92.7%), N.S. in 1 58/95 (61.1%), N.S. in 2
Other symptoms/signs fever rash	 65 (67%) 32/92 (34%); N.S. in 5
HHV-6 DNA on CSF by PCR qualitative PCR quantitative PCR median range (copies/ml)	 51/97 (53%) 46 (47%) 7615 (215 – 18000000)
CT scan, yes abnormal findings	69/97 (71%) 12/69 (17.4%)
MRI imaging, yes abnormal findings	81/97 (84%), 51/81 (63%)
Other viral infection (by PCR DNA-emia) before HHV-6 encephalitis (N° days) after HHV-6 encephalitis (N° days) Co-infection	 1 CMV (77), 1 ADV (99) 1 BKPyV (14), 1 ADV (26), 1 HHV-7 (26) 1 CMV
Median follow-up time (from encephalitis)	5.28 years, (95% C.I., 5.01-7.83)

Deaths, total number	72
Cause of death	
relapse/progression	11/72 (15%)
infectious	23 (32%)
non-infectious	33 (46%)
missing	5 (7%)
5-yr OS	24.7% (95% C.I., 17.1-35.6)

Legend.
HHV-6, Human Herpes Virus-6 encephalitis; M, male; F, female; Allo-HCT: allogeneic hematopoietic cell transplant; N.S.: not specified; CT, computed tomography; MRI, magnetic resonance imaging; CMV, cytomegalovirus; ADV, adenovirus; BKPyV, BK polyoma virus; HHV-7, human herpes virus-7; OS, overall survival; C.I., confidence interval

Table 2. Univariate analysis of risk factors for overall survival in patients with HHV-6 encephalitis

Variable	N	Overall N = 97	N° events	28 Days OS (95% C.I.)	90 Days OS (95% C.I.)	365 Days OS (95% C.I.)	HR	95% CI	p-value*
All	97		72	77% (69%, 86%)	55% (46%, 66%)	41% (32%, 52%)			
Sex	97								
M		66 (68%)	49	77% (68%, 88%)	58% (47%, 71%)	42% (32%, 56%)	1.00		
F		31 (32%)	23	77% (64%, 94%)	48% (34%, 70%)	39% (25%, 60%)	1.05	0.64, 1.73	0.8
Age class	97								
≤ 18 year		20 (21%)	11	90% (78%, 100%)	70% (53%, 93%)	55% (37%, 82%)	—	—	
>18 year		77 (79%)	61	74% (65%, 84%)	51% (41%, 63%)	38% (28%, 50%)	1.88	0.99, 3.58	0.055
Underlying disease	92								
AL - B-cell lymphoma		52 (57%)	36	79% (68%, 91%)	56% (44%, 71%)	40% (29%, 56%)	—	—	
Other		40 (43%)	33	78% (66%, 92%)	53% (39%, 70%)	40% (27%, 58%)	1.22	0.76, 1.96	0.4
Donor type	97								
Haplo		5 (5.2%)	4						
Identical sibling		4 (4.1%)	4			-			
Unrelated		88 (91%)	64	77% (69%, 87%)	57% (47%, 68%)	44% (35%, 56%)			

Variable	N	Overall N = 97	N° events	28 Days OS (95% C.I.)	90 Days OS (95% C.I.)	365 Days OS (95% C.I.)	HR	95% CI	p-value*
Stem cell source	97								
CB		21 (22%)	11	86% (72%, 100%)	76% (60%, 97%)	67% (49%, 90%)	1.00		
BM/PB		76 (78%)	61	75% (66%, 85%)	49% (39%, 61%)	34% (25%, 47%)	2.26	1.18, 4.33	0.014
Myeloablative conditioning regimen	95								
No		40 (42%)	34	73% (60%, 88%)	43% (30%, 61%)	28% (17%, 45%)	1.82	1.12-2.94	0.014
Yes		55 (58%)	37	80% (70%, 91%)	64% (52%, 78%)	51% (39%, 66%)	1.00		
Number of Allo-HCT	97								
1		92 (95%)	68	78% (70%, 87%)	55% (46%, 67%)	42% (33%, 54%)			
2		5 (5.2%)	4	60% (29%, 100%)	40% (14%, 100%)	20% (3.5%, 100%)			

Legend.
M, male; F, female; Allo-HCT, allogeneic hematopoietic cell transplantation; CB, cord blood; BM, bone marrow; PB, peripheral blood; Haplo, haploidentical