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Adenovirus infections after allogeneic hematopoietic cell transplantation in children and adults: a study from the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation

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JS, MM – design of the study; NK, LW, GT – preparing database; GT – statistical analysis, tables and figures; JS – writing manuscript; JS, MM, DA, SC, LG, PL, RdlC – analysis and critical revision of the paper; All authors – providing clinical data, revision and final approval of the paper.

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MM reports lecture fees and board meeting fees from Allovir, bioMérieux, Gilead, Janssen, Moderna, Mundipharma, Pfizer, all outside the submitted work. JAS declares consultancy for Medac, Jazz, Vertex and Kiadis Pharma in previous 24 months. All other Authors declared no conflict of interest.

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Adenovirus infections after allogeneic hematopoietic cell transplantation in children and adults: a study from the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation

ABSTRACT

The objective of the study was the analysis of clinical types, outcome and risk factors associated with outcome of adenovirus (ADV) infection, in children and adults after allo-HCT. Total number of 2529 patients (43.9% children; 56.1% adults) transplanted between 2000-2022 reported to the EBMT database with diagnosis of ADV infection were analyzed. ADV infection manifested mainly as viremia (62.6%) or gastrointestinal infection (17.9%). The risk of 1-year mortality was higher in adults ($p=0.0001$), and in patients with ADV infection developing before day +100 ($p<0.0001$). The 100-day overall survival after diagnosis of ADV infections was 79.2% in children and 71.9% in adults ($p<0.0001$). Factors contributing to increased risk of death by day +100 in multivariate analysis, in children: CMV-seropositivity of donor and/or recipient ($p=0.02$), and Lansky/Karnofsky score <90 ($p<0.0001$), while in adults: type of ADV infection (viremia or pneumonia vs gastrointestinal infection) ($p=0.0004$), second or higher HCT ($p=0.0003$), and shorter time from allo-HCT to ADV infection ($p=0.003$). In conclusion, we have shown that in patients infected with ADV, short-term survival is better in children than adults. Factors directly related to ADV infection (time, clinical type) contribute to mortality in adults, while pre-transplant factors (CMV-serostatus, Lansky/Karnofsky score) contribute to mortality in children.

INTRODUCTION

Adenovirus (ADV) infections contribute to morbidity and increased mortality after hematopoietic cell transplantation (HCT) [1, 2]. The clinical manifestations of ADV infections in HCT patients most frequently include upper respiratory disease, gastroenteritis, and kerato-conjunctivitis, while encephalitis, myocarditis, and pneumonia occur sporadically. Local infections can disseminate to cause systemic disease and/or progress to lethal disease [2]. Diagnostic and therapeutic management of infections with ADV in immunocompromised host was presented by several working groups [1-5].

Existing data suggest that the incidence of ADV infections in patients after HCT is higher in children than in adults [2, 4]. Recent data showed the incidence of ADV infections in 7.4% of children and 2.9% adults after allogeneic HCT (allo-HCT) [6], while this infection does not seem to be a major issue after CAR-T (chimeric antigen receptor T-cells) therapy [7, 8]. Further pediatric analysis showed incidence of ADV infections of 10.5% after allo-HCT and 1.3% after autologous HCT (auto-HCT) [9]. Recent US analysis showed the incidences of ADV infection, any ADV viremia, and ADV viremia ≥1000 copies/mL within 6 months after the allo-HCT in children to be 23%, 16%, and 9%, respectively, while for adults being 5%, 3%, and 2%, respectively [10]. Even higher rates were documented in AdVance study: 32% and 6% of cumulative incidence of ADV infection in children and adults, respectively; and the incidence of ADV viremia ≥1000 copies/mL was 14% and 1.5% in children and adult recipients, respectively [11, 12].

In this EBMT (European Society for Blood and Marrow Transplantaion) registry-based study we aimed to analyze the outcome of ADV infection in children and adults after allo-HCT, as well as clinical forms of ADV infection and risk factors associated with adverse outcome of ADV infection after allo-HCT.

METHODS

Study design. All patients with an allo-HCT performed between 2000-2022 reported to the EBMT database, who had ADV infection after HCT, were analyzed in this retrospective registry-based study.

Basic data of adenovirus infection including clinical type, diagnostics, therapeutic strategy, and outcome were analyzed. No exclusion criteria were implemented.

Data collection. Transplant data available on age, sex, primary diagnosis, type of donor, type of conditioning (reduced intensity conditioning [RIC] or myeloablative conditioning [MAC], according to the EBMT definitions), remission status of the underlying malignancy at allo-HCT, source of stem cells (i.e., peripheral blood [PB] or bone marrow [BM]), donor and recipient CMV (cytomegalovirus) serostatus, acute/chronic GVHD, concomitant infections, and outcome were analyzed. Acute graft-versus-host disease (aGVHD) was graded according to criteria of Glucksberg *et al* [13], chronic GVHD was graded as limited or extensive. This study was approved and performed by the Infectious Diseases Working Party (IDWP) of the EBMT in accordance with the principles of the Declaration of Helsinki.

Clinical diagnosis of ADV infection was done locally in transplant center and reported as: viremia, gastrointestinal infection, cystitis, pneumonia, hepatitis, central nervous system (CNS) infection, septic shock, multiorgan failure (MOF) or other.

Data set availability. Data represent results of registry-based study of patients with documented ADV infection. No personal data are included. With the retrospective registry-based design of the study, no ethical review board approval was necessary. Data set remains the property of EBMT. It can be available upon reasonable request to the corresponding author.

Ethical considerations. The study was conducted in accordance with the EBMT Guidelines for Retrospective Studies and the principles of the Declaration of Helsinki. EBMT Centres commit to obtain informed consent with the local regulations applicable at the time of transplantation in order to report pseudoanonymised data to the EBMT.

Statistical analysis. The primary endpoint was the probability of overall survival (OS) at day +30, at day +100, at 1 year after allo-HCT. OS was defined as the time from allo-HCT to last observation or death, regardless of the cause. OS was computed using the Kaplan-Meier estimator, with the log-rank test being used to perform univariate comparisons and the Greenwood formula to compute confidence intervals. Non-relapse mortality (NRM) was defined as death after transplant that was not preceded by recurrent or progressive primary disease. The cumulative incidence of acute, and chronic GVHD were estimated considering the corresponding type of GVHD as an event of interest and death without GVHD as a competing risk setting, with the Gray test being used to compare different groups and the delta method to obtain confidence intervals. Factors considered in risk factor analysis were gender, diagnosis, the patient's age at transplantation, the donor's age at transplantation, donor/recipient sex matching (female donor to male recipient vs other), type of donor (HLA-matched sibling vs other donor types), type of conditioning (reduced intensity conditioning, RIC; myeloablative conditioning, MAC), disease status at time of transplantation (i.e., first complete remission [CR] vs other), source of stem cells (peripheral blood, PB; bone marrow, BM; cord blood, CB), year of transplantation and CMV serostatus of recipient (seronegative vs seropositive), donor (seronegative vs seropositive), and donor/recipient combinations (seronegative/seronegative, seropositive/seronegative, seronegative/seropositive, seropositive/seropositive).

Comparisons for categorical variables were done using the Fisher's exact test or the χ^2 test. The proportional hazard assumption was verified using graphical methods: scaled Schoenfeld [14] residuals and graphical checks proposed by Klein-Moeschberger [15] were performed without finding evidence of relevant violations. The univariate and multivariate effect of variables on OS was analyzed using a Cox proportional hazards model in order to estimate hazard risks (HRs). All tests were two-sided, with the type I error rate fixed at 0.05. The Bonferroni correction was applied in the case of multiple subgroup comparisons. Median follow-up was calculated according to the inverted Kaplan-Meier technique [16]. All the analyses were performed using the statistical software SAS (SAS Institute Inc., Cary, NC, USA) version 9.2.

RESULTS

Demographics. There were 2529 patients transplanted between 2000-2022 with reported ADV infection. Patient and transplant characteristics are presented in **Table 1**. With respect to age, 43.9% (n=1110) were children (<18 years), and 56.1% (n=1419) were adults. Median age of patients was 23.6 (min-max: 0.1-74.0) years; 62.4% were male. Primary diagnosis: 55.4% (n=1401) acute leukemia (AL) or MDS, 20.9% (n=529) other malignant diseases, and 23.7% (n=599) non-malignant disorders. Stem cell source used for transplantation: peripheral blood (PB) in 51.7% (n=1308), bone marrow (BM) in 32.3% (n=818), cord blood (CB) in 15.6% (n=395), or their combinations in 0.4% (n=8). According to donor type, majority of patients had unrelated donor (63.2%), matched related donor (22.5%), mismatched related (14.3%). Conditioning: myeloablative in 59.0% (n=1491), RIC in 39.8% (n=1006), not determined in 1.3% (32). Total Body Irradiation (TBI) based conditioning was used in 32.0% (n=810) patients. Grade 2-4 acute GVHD was diagnosed in 44.6%, chronic GVHD in 33.6% (limited in 17.3%, extensive in 16.3%) of eligible patients.

Clinical manifestations of ADV infection. Viremia was diagnosed in 62.6% (n=1589), gastrointestinal infection in 17.9% (n=453), cystitis in 3.7% (n=94), pneumonia in 4.9% (n=124), and other not specified in 9.7% (n=246) patients, while number of reported cases of hepatitis, CNS infection, septic shock, and multiorgan failure (MOF) was below 10 for each complication.

Survival after ADV infection. Overall survival of entire cohort of patients infected with ADV was 88.7% (95%CI-87.4-89.9) at day +30, 75.1% (95%CI=73.3-76.7) at day +100, and 61.1% (59.1-63.0) at 1 year (**Figure 1AB**). Patients infected with ADV within 30 days after HCT had lower OS and higher NRM at day +100 (**Figure 1CD**). The 100-day overall survival (OS) after diagnosis of ADV infections was 79.2% (95%CI=76.6-81.5) in children and 71.9% (95%CI=69.4-74.2) in adults (p<0.0001) (**Figure 1E, Table 2**). With respect to clinical form of ADV disease, the 100-day OS was 82.3% in patients with gastrointestinal infection, 73.8% with viremia, and 66.3% patients with pneumonia (p=0.001). Patients with disseminated multiorgan disease had poor outcome; 3/7 septic shock and 6/6 with MOF died by day 100.

With respect to chronic GVHD the 1-year OS was 54.7% (95%CI=46.3-62.4) in patients with extensive chronic GVHD and 65.0% (95%CI=62.9-67.1) without cGVHD or with limited form of cGVHD (p=0.01).

In order to show a change in infection management over time (2000-2010 vs 2011-2022) we analyzed NRM in respective periods. The 100-day NRM probability was 27.7% (95%CI=24.5-31.0) between 2000-2010 and 18.7% (95%CI=16.8-20.5) between 2011-2022 (p<0.0001) (**Figure 1F**).

Risk factor analysis for overall survival. In multivariate analysis, factors contributing to worse OS at day +100 in all analyzed patients with ADV infection were: age >18 years, type of ADV infection (pneumonia and viremia), diagnosis of acute leukemia or MDS, second or higher HCT, PB or CB stem cell source, time from HCT to ADV infection <100 days and Karnofsky/Lansky score <90 (data not shown). When age was analyzed as continuous variable, a 10-years increase in age was an adverse risk factor for survival with HR=1.11 (95%CI=1.08-1.14), p<0.0001.

Since the risk of mortality was higher in adults at day +100 (HR=1.48, 95%CI=1.23-1.77; p<0.0001), and also at 1-year (HR=1.48, 95%CI=1.21-1.81; p<0.0001), the risk factors analysis was performed separately for children and adults (**Table 3**).

Factors contributing to increased risk of death by day +100 in children infected with ADV in univariate analysis were: type of ADV infection (viremia vs gastrointestinal infection), CMV seropositivity of donor or recipient, second or higher HCT, stem cell source (PB vs BM), *ex vivo* T-cell depletion, and Lansky/Karnofsky score <90. In multivariate analysis, two factors retained significance: CMV seropositivity of donor and/or recipient (p=0.02), and Lansky/Karnofsky score <90 (p<0.0001).

Factors contributing to increased risk of death by day +100 in adults infected with ADV in univariate analysis were: type of ADV infection (viremia or pneumonia vs gastrointestinal infection), second or higher HCT, shorter time from HCT to ADV infection (<30 days), and Karnofsky score <90. In multivariate analysis, three factors were significant: type of ADV infection (viremia or pneumonia vs gastrointestinal infection) (p=0.0004), second or higher HCT (p=0.0003), and shorter time from HCT to ADV infection (p=0.003).

CMV coinfections. In this cohort of patients infected with ADV, the proportion of CMV-seropositive (46.3% children vs 60.2% adults) and CMV-seronegative (46.6% children vs 36.7% adults) recipients reflected general population trend with higher rate of CMV-seropositivity in adults. Recipient and/or donor CMV-seropositivity in patients infected with ADV contributed to worse 100-days overall survival in children, but not in adults (Table 3). Overall, 868/2511 (34.6%) patients had CMV reactivation before diagnosis of ADV infection. Overall survival at 100 days and 1 year after ADV infection, as well as cumulative incidence of NRM did not differ between CMV-infected and CMV non-infected patients (**Figure 1GH**).

Causes of deaths. Out of 2529 analyzed patients infected with ADV, 938 (37.1%) patients died within 1 year after ADV infection, including 339 children (30.5% of total number of children) and 599 adults (42.2% of total number of adults) (OR=1.7, 95%CI=1.4-2.0; p<0.0001). Death rate from relapse, progression or secondary malignancy at 1 year was 6.3% in children and 8.5% in adults (OR=1.4, 95%CI=1.02-1.9; p=0.0359). Non-relapse mortality rate was 24.2% in children and 33.7% in adults (OR=1.6, 95%CI=1.3-1.9; p<0.0001). Infection-related deaths were reported in 12.0% children and 13.3% adults (ns). Deaths from ADV infection were reported in 16 children (1.4% of all patients; 4.7% of all deaths in pediatric population) and 12 adults (0.8% of all patients; 2.0% of all deaths in adult population) (ns).

DISCUSSION

Adenovirus infection results in a wide array of clinical presentations [2, 3]. In immunocompetent individuals ADV usually causes mild disease, while severe and life-threatening infections can occur in the immunocompromised populations, such as allo-HCT patients [17, 18].

This study aimed to analyze clinical manifestations and outcome of ADV infections after allo-HCT in children and adults. The most frequent clinical forms of ADV infection were viremia (63.1%), and gastrointestinal infection (16.9%), while pneumonia and cystitis contributed to 4.9% and 3.7%, respectively. Patients with ADV viremia or pneumonia had significantly lower survival in comparison to patients with other clinical manifestations. Since gastrointestinal infection can progress to systemic viremia, the role of fecal screening in children should be underlined to identify the need of pre-emptive therapy in order to prevent progression to viremia.

In spite of only about 20% of allo-HCT being performed in children [19], 43.9% of reported ADV infections occurred in children. This shows that ADV infection is a much more frequent problem in children than in adults. Overall survival was significantly higher in children than in adults at each time point: OS at day +100 after ADV diagnosis was higher in children than adults (79.2% vs 71.9%) and the risk of 1 year mortality was also higher in adults. These figures might reflect not only better survival from ADV infections in children, but also overall better post-transplant survival in children than adults. Undoubtedly, the impact of age itself of patients with ADV infection was a continuous risk factor for worse survival, reaching risk of 11% by each decade of life. Apart from age of patients, we found several major adverse risk factors for overall survival of patients with ADV infection. Interestingly, several differences between children and adults were observed.

Certain findings in our study translated to poorer outcomes. We focused on short-term outcome on 100 days, as this parameter is more closely related to clinical course of ADV infection than outcome at one year. Two factors contributed to poorer survival in children: CMV-seropositivity of donor and/or

recipient, and Lansky/Karnofsky score <90. Three factors contributed to poorer survival in adults: ADV viremia or pneumonia, second or higher HCT, and shorter time from allo-HCT to ADV infection (both <30 days, and <100 days). It shows that factors directly related to ADV infection, such as early infection or viremia or pneumonia contribute to mortality in adults but not in children. On the other hand, pre-transplant factors such as CMV-seropositivity or overall general performance score, but not factors related to ADV infection, contribute to mortality in children. Possible explanations include that children might face ADV infections more often than adults, but the survival is better in children than adults.

CMV seropositivity of donor and/or recipient (p=0.02) was a significant adverse risk factor in children with ADV infection, but not in adults, which provides further evidence that CMV seropositivity negatively influences transplant outcomes, a well-known factor in transplant setting [20]. Recently, it has been shown to have adverse impact in patients infected with SARS-CoV-2 [21].

Lansky/Karnofsky performance score <90 was a significant adverse factor for children with ADV infection (p<0.0001) in multivariate analysis, while for adults this was significant in univariate analysis only. Performance status is an important factor for survival after transplant and usually reflects presence of comorbidities [21].

Clinical type of ADV infection had a significant effect on survival in multivariate analysis in adults, with an adverse impact of ADV viremia or pneumonia in comparison to gastrointestinal infection (p=0.0004). In children, viremia had an adverse effect, when compared to gastrointestinal infection, but in univariate analysis only. This finding underlines low risk of severe complications in ADV-driven gastrointestinal infection. Based on recent reports, gut infection seems to be the most frequent clinical manifestation of ADV infection in transplant patients [5, 22].

Second or higher HCT had adverse impact in adults in multivariate analysis (p=0.0003), while in children was significant in univariate analysis only. This observation is in line with knowledge on the worse transplant outcome in advances stages of disease, usually related to relapse of primary disease [23].

Finally, shorter time from transplant to ADV infection had significant adverse impact on survival in adults (p=0.003). This was particularly evident if ADV infection appeared within the first 30 days after HCT, as shown on Figure 1E. Surprisingly, this effect was not observed in children, even in univariate analysis. This data supports consideration of screening for ADV viremia in the first 100 days regardless of age, especially as ADV infection seems not to be a major problem in adult patients after day +100.

With respect to changes over calendar time, the 100-day NRM decreased from 27.7% between 2000-2010 to 18.7% between 2011-2022, underlining the progress in management of infection. However, shifts or progression in clinical course of infection, diagnostic and therapeutic strategies were not analyzed in this study.

This is one of the largest ever study of patients with ADV infection after allo-HCT. It underlines several important and practical findings. Two prognostic factors were related to ADV infection: clinical form of ADV manifestation, and time from HCT to ADV infection. Other factors identified are well known associations of overall survival after allo-HCT, including bone marrow as a more frequent source of stem cells in children than in adults, which may have influenced better survival in children [24].

It was shown recently that additional ADV-related factors can contribute to overall survival in patients with ADV infection after HCT. Peak ADV viral load and ADV time-averaged area under the curve (AAUC) correlated with non-relapse mortality in T-cell depleted HCT and in pediatric patients, what supports the potential utility of ADV viral kinetics as endpoints in clinical analyses of ADV therapies

[25, 26]. With increased ADV disease burden, there was an increased risk of mortality after both autologous and allogeneic HCT [27].

Our study has some limitations. Retrospective data, collected from the registry are imperfect, with quantitative and repeated data on blood ADV-DNA being not available. Moreover, the study covered relatively long period of inclusion, thus different diagnostic and therapeutic strategies were implemented in participating centers. There is also a possibility of a bias towards higher number of children being reported, reflecting maybe that screening in children is more often routinely used than in adults.

In conclusion, we have shown that in patients infected with ADV, short-term 100-day overall survival and non-relapse survival are better in children than adults. Factors directly related to ADV infection, such as early infection or viremia or pneumonia contribute to mortality in adults but not in children, while pre-transplant factors such as CMV-seropositivity or overall general performance score, but not factors directly related to ADV infection, contribute to mortality in children. Results of this study might justify the need of regular screening both in children and adults.

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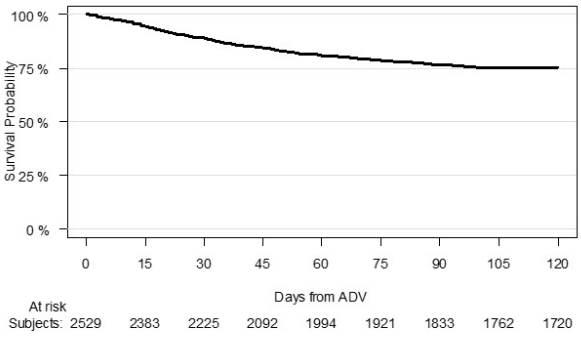
Figure and Tables legends:

Figure 1. Survival probability: (A) OS for all patients; (B) 100-day NRM for all patients; (C) OS according to time from HCT to ADV infection up to day 30; (D) 100-day NRM according to time from HCT to ADV infection up to day 30; (E) OS in children and adults; (F) 100-day NRM according to calendar time of transplant; (G) OS according to CMV reactivation before ADV infection; (H) 100-day NRM according to CMV reactivation before ADV infection.

Table 1. Main characteristics of patients with ADV infection, with comparison of characteristics between children and adults.

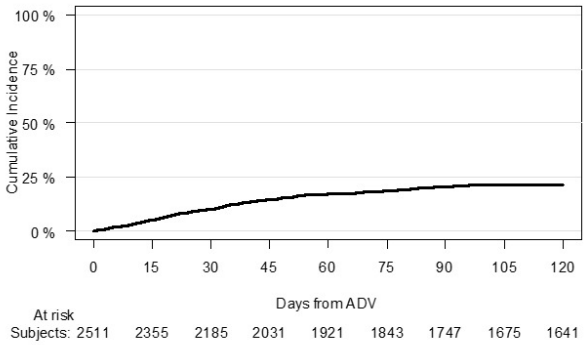
Table 2. Overall survival in all patients with ADV infection (Kaplan-Meier analysis)

Table 3. Univariate and multivariate analysis of 100-day overall survival in children and adults (in Cox model).



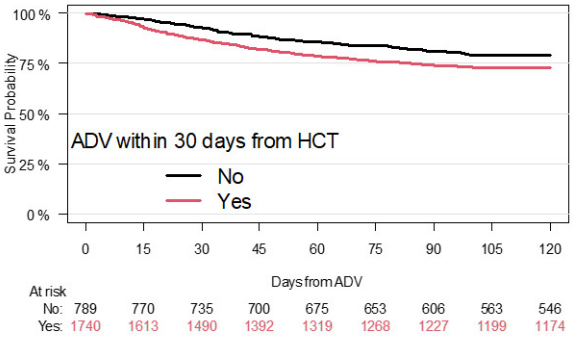
A

Patients	1-year death	30-days	100-day
2529	938	88.7 (87.4-89.9)	75.1 (73.3-76.7)



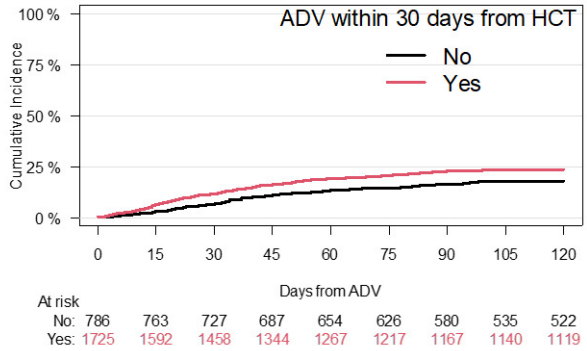
B

Patients	100-day NRM events	100-day NRM probability
2511	530	21.5 (19.9-23.1)



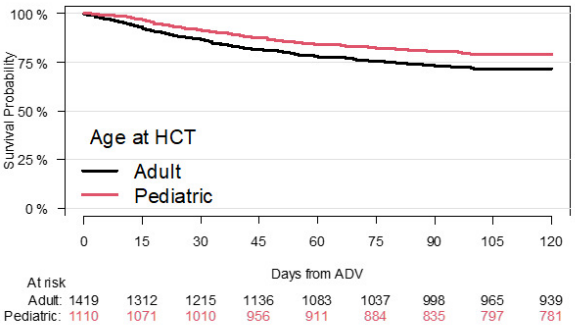
C

Days from HCT to ADV	Patients	6-week OS event	8-week OS event	6-week OS probability	8-week OS probability
<30	1740	297	354	82.7 (80.8-84.4)	79.3 (77.3-81.2)
≥30	789	83	108	89.5 (87.1-91.4)	86.3 (83.7-88.5)
					p<0.0001



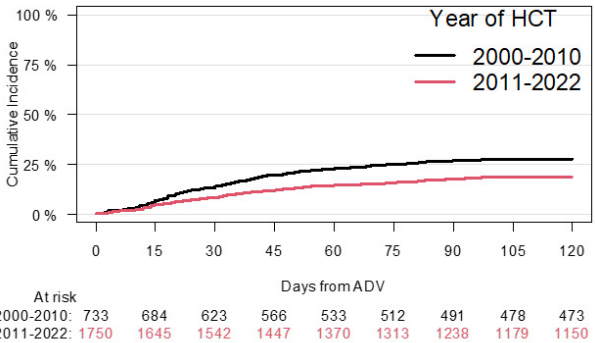
D

Days from HCT to ADV	Patients	100-day NRM event	100-day NRM probability
<30	1725	392	23.2 (21.2-25.3)
≥30	786	138	17.8 (15.2-20.5)
			p=0.001



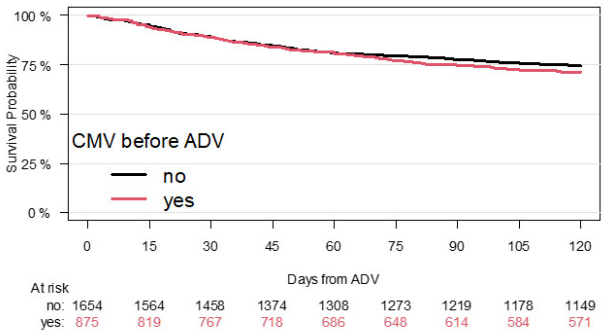
E

AGE	Patients	1-year death	30-day OS	100-day OS
<18 yrs	1110	339	91.5 (89.7-93.0)	79.2 (76.6-81.5)
≥18 yrs	1419	599	86.5 (84.6-88.2)	71.9 (69.4-74.2)
				p<0.0001



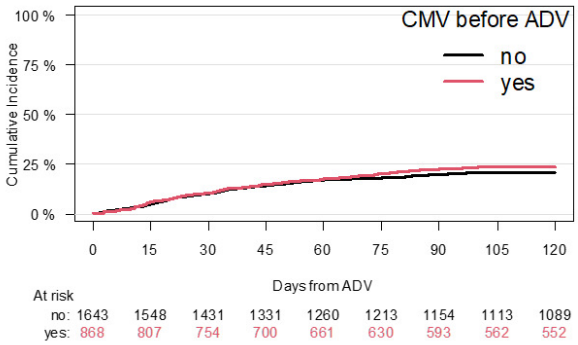
F

Year of HCT	Patients	100-day NRM event	100-day NRM probability
2000-2010	733	203	27.7 (24.5-31.0)
2011-2022	1750	318	18.7 (16.8-20.5)
			p<0.0001



G

CMV before ADV	Patients	1-year death	100-day OS	1-year OS
Yes	875	342	72.9 (69.9-75.8)	58.8 (55.4-62.2)
No	1654	596	76.3 (74.2-78.3)	62.3 (59.9-64.7)
				p=0.1



H

CMV before ADV	Patients	100-day NRM event	100-day NRM probability
Yes	868	197	20.6 (18.7-22.6)
No	1643	333	23.2 (20.4-26.1)
			P=0.2

Table 1. Main characteristics of patients with ADV infection, with comparison of characteristics between children and adults.

	Total (N=2529)	**Children (N=1110)**	**Adults (N=1419)**	**p**
Sex				
Male	1579 (62.4)	691 (62.3)	888 (62.6)	0.9
Female	950 (37.6)	419 (37.7)	531 (37.4)	
Diagnosis (1)				
Acute leukemia	1099 (43.5)	472 (42.5)	627 (44.2)	
Chronic leuaemia	113 (4.5)	9 (0.8)	104 (7.3)	
Lymphoma	301 (11.9)	21 (1.9)	280 (19.7)	
Plasma cell disorders	109 (4.3)	0 (0.0)	109 (7.7)	
Solid tumours	6 (0.2)	6 (0.5)	0 (0.0)	
Myelodysplastic/Myeloproliferative diseases	302 (11.9)	85 (7.7)	217 (15.3)	
Bone marrow failure	215 (8.5)	151 (13.6)	64 (4.5)	
Inborn errors of metabolism or immunity	267 (10.6)	257 (23.2)	10 (0.7)	
Histiocytic disorders	41 (1.6)	39 (3.5)	2 (0.1)	
Auto-immune diseases	6 (0.2)	3 (0.3)	3 (0.2)	
Hemoglobinopathies	70 (2.8)	67 (6.0)	3 (0.2)	
Diagnosis (2)				
ALL/AML/MDS	1401 (55.4)	557 (50.2)	844 (59.5)	<0.0001
Non malignant	599 (23.7)	517 (46.6)	82 (5.8)	
Other malignant	529 (20.9)	36 (3.2)	493 (34.7)	
Age at the diagnosis				
Median	17.2	3.4	41.7	NA
Min-Max	0.0 - 73.3	0.0 - 17.4	0.0 - 73.3	
N obs	2021	977	1044	
Time from HCT to ADV infection (months) (1)				
Median	1.9	1.1	2.7	<0.0001
Min-Max	0.0 - 150.8	0.0 - 93.6	0.0 - 150.8	
N obs	2529	1110	1419	
Time from HCT to ADV infection (2)				
<30 days	789 (31.2)	503 (45.3)	286 (20.2)	<0.0001
>30 days	1740 (68.8)	607 (54.7)	1133 (79.8)	
<60 days	1296 (51.2)	760 (68.5)	536 (37.8)	<0.0001
>60 days	1233 (48.8)	350 (31.5)	883 (62.2)	
Age at HCT				
Median	23.6	6.3	44.8	NA
Min-Max	0.1 - 74.0	0.1 - 18.0	18.1 - 74.0	
N obs	2529	1110	1419	
Stem cell source				
BM (bone marrow) ± other sources	826 (32.7)	602 (54.2)	224 (15.8)	<0.0001
PB (peripheral blood)	1308 (51.7)	236 (21.3)	1072 (75.5)	
CB (cord blood)	395 (15.6)	272 (24.5)	123 (8.7)	
Type of donor (1)				
Identical sibling	540 (21.4)	187 (16.8)	353 (24.9)	
Syngeneic	2 (0.1)	1 (0.1)	1 (0.1)	
Matched other relative	25 (1.0)	21 (1.9)	4 (0.3)	
Matched unrelated	201 (7.9)	90 (8.1)	111 (7.8)	
Mismatched relative	362 (14.3)	154 (13.9)	208 (14.7)	
Mismatched unrelated	190 (7.5)	86 (7.7)	104 (7.3)	
Unrelated	1209 (47.8)	571 (51.4)	638 (45.0)	

	Total (N=2529)	**Children (N=1110)**	**Adults (N=1419)**	**p**
Type of donor (2)				0.0002
Matched related	567 (22.4)	209 (18.8)	358 (25.2)	
Mismatched relative	362 (14.3)	154 (13.9)	208 (14.7)	
Unrelated	1600 (63.3)	747 (67.3)	853 (60.1)	
Number of HCT				
First	2023 (80.0)	979 (88.2)	1044 (73.6)	<0.0001
Second or higher	506 (20.0)	131 (11.8)	375 (26.4)	
Conditioning regimen				
Standard myeloablative (MAC)	1491 (59.0)	891 (80.3)	600 (42.3)	<0.0001
Reduced intensity (RIC)	1006 (39.8)	205 (18.5)	801 (56.4)	
missing	32 (1.3)	14 (1.2)	18 (1.3)	
TBI (Total Body Irradiation)				
no	1700 (67.2)	785 (70.7)	915 (64.5)	0.0004
yes	810 (32.0)	313 (28.2)	497 (35.0)	
missing	19 (0.8)	12 (1.1)	7 (0.5)	
Karnofsky/Lansky* Performance Score				
Median	90.0	90.0	90.0	0.3
Range	10.0 - 100.0	10.0 - 100.0	40.0 - 100.0	
N obs	1972	789	1183	
CMV serostatus (recipient / donor)				
-/-	734 (29.0)	345 (31.1)	389 (27.4)	<0.0001
-/+	304 (12.0)	172 (15.5)	132 (9.3)	
+/-	515 (20.4)	206 (18.6)	309 (21.8)	
+/+	853 (33.7)	308 (27.7)	545 (38.4)	
missing	123 (4.9)	79 (7.1)	44 (3.1)	
Neutrophil engraftment				
No engraftment	47 (1.9)	32 (2.9)	15 (1.1)	0.001
Engraftment	1626 (64.3)	718 (64.7)	908 (64.0)	
Lost graft	17 (0.7)	13 (1.2)	4 (0.3)	
Missing / unknown / not applicable	839 (33.2)	347 (31.3)	492 (34.6)	
In vivo T-cell depletion				
No	669 (26.5)	247 (22.3)	422 (29.7)	<0.0001
Yes	1561 (61.7)	846 (76.2)	715 (50.4)	
Missing	299 (11.8)	17 (1.5)	282 (19.9)	
Ex vivo T-cell depletion				
No	1986 (78.5)	935 (84.2)	1051 (74.1)	<0.0001
Yes	205 (8.1)	134 (12.1)	71 (5.0)	
Missing	338 (13.4)	41 (3.7)	297 (20.9)	
Acute GVHD				
No (0/I°)	1328 (52.5)	601 (54.1)	727 (51.2)	0.16
Yes (II-IV°)	1129 (44.6)	479 (43.2)	650 (45.8)	
grade unknown	31 (1.2)	6 (0.5)	25 (1.8)	
missing	41 (1.6)	24 (2.2)	17 (1.2)	
Infectious complications (other than ADV)				
No	116 (4.6)	24 (2.2)	92 (6.5)	<0.0001
Yes	2308 (91.2)	1033 (93.1)	1275 (89.8)	
Missing	105 (4.2)	53 (4.8)	52 (3.7)	
Non-infectious complications				
No	1076 (42.5)	436 (39.3)	640 (45.1)	0.01
Yes	1198 (47.4)	549 (49.5)	649 (45.8)	
missing	255 (10.1)	125 (11.3)	130 (9.2)	

	Total (N=2529)	Children (N=1110)	Adults (N=1419)	p
Chronic GVHD (on 2196 patients alive at day +100)				
no	1271 (57.9)	669 (70.7)	602 (48.2)	<0.0001
limited	379 (17.3)	110 (11.6)	269 (21.5)	
extensive	357 (16.3)	96 (10.1)	261 (20.9)	
missing	189 (8.6)	71 (7.5)	118 (9.4)	
Type and localization of ADV infection (first episode)				
Viremia	1582 (62.6)	741 (66.8)	841 (59.3)	
Gastrointestinal infection	453 (17.9)	222 (20.0)	231 (16.3)	
Cystitis	94 (3.7)	16 (1.4)	78 (5.5)	
Pneumonia	124 (4.9)	34 (3,1)	90 (6.4)	
Hepatitis	7 (0.3)	3 (0.3)	4 (0.3)	
CNS (Central Nervous System) infection	7 (0.3)	2 (0.2)	5 (0.4)	
Septic shock	7 (0.3)	2 (0.2)	5 (0.4)	
Multiorgan failure (MOF) due to infection	6 (0.2)	6 (0.5)	0 (0.0)	
Other not specified	249 (9.8)	84 (7.6)	165 (11.6)	

(*) Lansky score for patients up to 16 years; Karnofsky score for patients >16 years

Table 2. Overall survival in all patients with ADV infection (Kaplan-Meier analysis)

	Patients	30-day death	100-day death	1-year death	30-day OS	100-day OS	1-year OS	p
Total	2529	284	618	938	88.7 (87.4-89.9)	75.1 (73.3-76.7)	61.1 (59.1-63.0)	-
Type of infection *(total)*								
Viremia	1582	189	407	610	88.0 (86.3-89.5)	73.8 (71.5-75.9)	59.6 (57.1-62.0)	0.001*
Gastrointestinal infection	453	21	78	146	95.3 (92.9-96.9)	82.3 (78.4-85.5)	65.5 (60.8-69.9)	
Cystitis	94	12	29	42	87.2 (78.6-92.5)	68.5 (57.9-76.9)	53.2 (42.3-63.0)	
Pneumonia	124	27	37	47	76.8 (67.00-84.1)	66.3 (55.8-74.8)	59.0 (48.2-68.3)	
Hepatitis	7	5	6	6				
CNS infection	7	5	5	5				
Septic shock	7	2	3	3				
Multiorgan failure due to infection	6	3	6	6				
Other not specified	246	20	46	71	91.7 (87.5-94.6)	80.8 (75.2-85.2)	69.7 (63.3-75.2)	
Type of infection (*Children only*)								
Viremia	741	66	164	243	91.1 (88.8-92.9)	77.4 (74.1-80.3)	65.4 (61.7-68.8)	0.01*
Gastrointestinal infection	222	7	27	48	96.8 (93.4-98.5)	87.4 (82.2-91.2)	76.6 (70.1-81.8)	
Cystitis	16	3	4	9				
Pneumonia	34	4	6	8	83.3 (61.5-93.4)	74.8 (52.2-87.8)	74.8 (52.2-87.8)	
Hepatitis	3	2	3	3				
CNS infection	2	0	0	0				
Septic shock	2	1	1	1				
Multiorgan failure due to infection	6	3	6	6				
Other not specified	84	8	15	21	90.2 (81.3-94.9)	81.4 (71.0-88.3)	73.4 (62.2-81.8)	
Type of infection *(Adults only)*								
Viremia	841	123	243	367	85.3 (82.7-87.5)	70.6 (67.4-73.6)	54.6 (51.0-57.9)	0.04*
Gastrointestinal infection	231	14	51	98	93.9 (89.9-96.3)	77.4 (71.4-82.3)	55.3 (48.4-61.6)	
Cystitis	78	9	25	33	88.4	67.2	55.5	

					(78.9-93.8)	(55.4-76.5)	(43.4-66.1)	
Pneumonia	90	23	31	39	74.6 (62.8-83.2)	63.4 (51.1-73.4)	54.3 (41.9-65.1)	
Hepatitis	4	3	3	3				
CNS infection	5	5	5	5				
Septic shock	5	1	2	2				
Other not specified	162	12	31	50	92.5 (87.2-95.7)	80.4 (73.4-85.8)	67.7 (59.7-74.5)	
Patient sex								
Male	1579	190	401	589	87.9 (86.2-89.4)	74.1 (71.9-76.2)	61.1 (58.6-63.5)	0.7
Female	950	94	217	349	90.0 (87.9-91.8)	76.7 (73.8-79.3)	61.1 (57.8-64.2)	
Age								
< 18 years	1110	94	226	339	91.5 (89.7-93.0)	79.2 (76.6-81.5)	67.7 (64.8-70.5)	<0.0001
≥ 18 years	1419	190	392	599	86.5 (84.6-88.2)	71.9 (69.4-74.2)	56.0 (53.3-58.6)	
Diagnosis								
ALL/AML/MDS	1401	159	355	555	88.6 (86.8-90.1)	74.2 (71.8-76.4)	58.4 (55.7-61.0)	<0.0001
Non malignant	599	47	112	156	92.1 (89.6-94.0)	80.9 (77.4-83.8)	72.5 (68.6-76.0)	
Other malignant	529	78	151	227	85.2 (81.8-87.9)	71.0 (66.9-74.7)	55.7 (51.3-59.9)	
CMV serostatus donor/recipient								
+/+	853	99	225	328	88.3 (85.9-90.3)	72.9 (69.8-75.8)	59.1 (55.6-62.5)	0.1
+/-	515	61	127	198	88.0 (84.9-90.6)	74.8 (70.7-78.3)	59.3 (54.8-63.6)	
-/+	304	33	69	107	89.1 (85.1-92.2)	77.1 (71.9-81.4)	63.7 (57.8-68.9)	
-/-	734	75	161	254	89.7 (87.3-91.7)	77.7 (74.5-80.6)	64.2 (60.5-67.6)	
Number of HCT								
First	2023	192	442	689	90.4 (89.1-91.7)	77.7 (75.8-79.5)	64.1 (61.8-66.2)	<0.0001
Second or higher	506	92	176	249	81.7 (78.0-84.8)	64.7 (60.4-68.8)	49.5 (45.0-53.9)	

Stem cell source								
BM (±other sources)	826	69	158	227	91.6 (89.5-93.3)	80.5 (77.6-83.0)	71.1 (67.8-74.2)	<0.0001
CB	395	42	98	153	89.4 (85.9-92.0)	74.9 (70.3-78.9)	59.9 (54.8-64.6)	
PB	1308	173	362	558	86.7 (84.7-88.4)	71.8 (69.2-74.1)	55.3 (52.4-58.0)	
Conditioning regimen								
RIC	1006	126	267	407	87.4 (85.2-89.3)	72.9 (70.0-75.6)	57.6 (54.4-60.7)	0.006
MAC	1491	156	345	521	89.5 (87.8-90.9)	76.4 (74.1-78.5)	63.3 (60.7-65.8)	
TBI-based conditioning								
No	1700	189	404	611	88.8 (87.2-90.2)	75.8 (73.6-77.8)	62.3 (59.8-64.6)	0.1
Yes	810	94	210	320	88.3 (85.9-90.3)	73.6 (70.4-76.5)	58.7 (55.1-62.1)	
***In vivo* T-cell depletion**								
No	669	64	136	226	90.4 (87.9-92.4)	79.3 (76.0-82.2)	64.0 (60.1-67.6)	0.2
Yes	1561	166	382	571	89.3 (87.7-90.7)	75.0 (72.8-77.1)	61.7 (59.1-64.1)	
***Ex vivo* T-cell depletion**								
No	1986	197	445	690	90.0 (88.6-91.3)	77.1 (75.2-78.9)	63.3 (61.1-65.5)	0.006
Yes	205	28	60	91	86.3 (80.7-90.3)	70.2 (63.3-76.0)	54.0 (46.7-60.7)	

*Comparison of the 5 categories with an acceptable sample size.

Table 3. Univariate and multivariate analysis of 100-day overall survival in children and adults (in Cox model).

	CHILDREN						ADULTS					
	n	**deaths**	**Univariate analysis**		**Multivariate analysis**		**n**	**deaths**	**Univariate analysis**		**Multivariate analysis**	
Variables			**HR (95% CI)**	**p**	**HR (95% CI)**	**p**			**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Type of ADV infection**				0.027*						0.004*		0.0004
Viremia	741	164	1.93 (1.28-2.90)				841	243	1.41 (1.04-1.91)		1.76 (1.20-2.58)	
GI infection	222	27	1.00				231	51	1.00		1.00	
Cystitis	16	4	2.37 (0.83-6.79)				78	25	1.57 (0.98-2.54)		2.05 (1.20-3.53)	
Pneumonia	24	6	2.31 (0.95-5.58)				72	26	1.98 (1.23-3.17)		2.90 (1.63-5.17)	
Other	82	15	1.57 (0.83-2.94)				162	31	0.86 (0.55-1.35)		1.03 (0.60-1.77)	
Patient sex												
Male	691	142	1.00				888	259	1.00			
Female	419	84	0.98 (0.75-1.29)	0.9			531	133	0.83 (0.67-1.02)	0.08		
Diagnosis				0.08*						0.6*		
AML/ALL/MDS	557	129	1.36 (1.04-1.78)				844	226	1.01 (0.65-1.56)			
Other malignant	36	7	1.11 (0.51 -2.40)				493	144	1.12 (0.71 -1.75)			
Non malignant	517	90	1.00				82	22	1.00			
CMV serostatus R/D				0.08*						0.3*		
-/-	345	53	1.00		1.00	0.02	389	108	1.00			
+/+	308	66	1.45 (1.01-2.08)		1.56 (1.04-2.32)		545	159	1.07 (0.84-1.36)			
+/-	206	45	1.50 (1.01-2.23)		1.59 (1.03-2.45)		309	82	0.94 (0.71-1.26)			
-/+	172	41	1.61 (1.07-2.42)		1.96 (1.26-3.02)		132	28	0.73 (0.48-1.11)			
Number of HCT												
First	979	184	1.00				1044	258	1.00		1.00	
≥Second	131	42	1.82 (1.31-2.55)	0.0004			375	134	1.58 (1.28-1.95)	<0.0001	1.91 (1.34-2.72)	0.0003

Stem cell source				0.016*						0.4*		
BM	602	104	1.00				224	54	1.00			
CB	272	61	1.30 (0.95-1.79)				123	37	1.26 (0.83-1.92)			
PB	236	61	1.57 (1.15-2.16)				1072	301	1.21 (0.90-1.61)			
Conditioning regimen												
RIC	205	44	1.11 (0.80-1.55)	0.5			801	223	0.99 (0.81-1.21)	0.9		
MAC	891	178	1.00				600	167	1.00			
TBI in conditioning												
No	785	156	1.00				915	248	1.00			
Yes	313	68	1.11 (0.83-1.47)	0.5			497	142	1.06 (0.86-1.30)	0.6		
***In vivo* T-cell depletion**												
No	247	39	1.00				422	97	1.00			
Yes	846	180	1.40 (0.99-1.97)	0.06			715	202	1.26 (0.99-1.61)	0.06		
***Ex vivo* T-cell depletion**												
No	935	176	1.00	0.04			1051	269	1.00	0.07		
Yes	134	35	1.46 (1.02-2.10)				71	25	1.47 (0.97-2.21)			
Time from HCT to ADV infection												
<100 days	929	195	1.26 (0.86-1.85)	0.2			810	255	1.46 (1.19-1.80)	0.0003	1.49 (1.15-1.92)	0.003
≥100 days	181	31	1.00				609	137	1.00		1.00	
Lansky/Karnofsky#												
<90	443	124	1.97 (1.50-2.58)	<0.0001	1.95 (1.45-2.62)	<0.0001	477	157	1.34 (1.09-1.65)	0.005		
≥90	589	90	1.00		1.00		872	233	1.00			

HR>1 refers to higher mortality; *overall comparison; ** Multivariate analysis performed on the following infections: Viremia, Gastrointestinal infection, Cystitis, Pneumonia, Other; (#) Lansky score for patients up to 16 years; Karnofsky score for patients >16 years