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Occurrence, risk factors and outcome of adenovirus infection in adult recipients of allogeneic hematopoietic stem cell transplantation

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ABSTRACT

Background: Adenovirus (ADV) infections can have a high mortality in immunocompromised patients and are difficult to treat.
Objectives and study design: We retrospectively analyzed occurrence and risk factors of ADV infection in 399 adults with hematological disorders undergoing hematopoietic stem cell transplantation (allo-HSCT), focusing on alternative donor transplantation (ADT) and disseminated disease.
Results: ADV infection occurred in 42 patients (10.5%). Disease was localized in 18 and disseminated in 6 patients. ADV infection was observed in 15% after ADT, performed in 29% of all recipients, and was less frequent (6%) in T-cell-replete (TCR) haploidentical transplantation using post-transplantation cyclophosphamide (PTCY) than in other ADT protocols. Lower age, the use of alternative donor grafts and acute graft-versus-host disease (GvHD) ≥ grade II were risk factors for ADV infection.

After failure of standard antiviral treatment, three patients with disseminated ADV disease received one dose of ADV-specific T cells, resulting in virological response in 2/3 patients, clearance of ADV viremia in 2/2 patients, and survival of 1/3 patients; both patients with pneumonia died.
Conclusions: ADV infection was of moderate occurrence in our adult recipients of allo-HSCT despite a high proportion of potential high-risk patients receiving ADT. TCR strategies using PTCY might limit ADV complications in haploidentical transplantation. Despite feasible adoptive therapy strategies, outcome of disseminated disease remains dismal.

1. Background

Infection hampers the success of allogeneic hematopoietic stem cell transplantation (allo-HSCT), in particular viral complications in recipients of HLA-mismatched grafts [1]. In children, adenovirus (ADV) commonly causes severe morbidity and mortality after allo-HSCT [2] while incidence of ADV infection in adult patients is lower [3,4]. ADV infection can be asymptomatic or can result in localized or disseminated disease. ADV pneumonia and dissemination of disease carry a high mortality of up to 80% in recipients of allogeneic grafts [2,5]. Main risk factors for ADV infection are severe graft-versus-host disease (GvHD), different forms of HLA-mismatched transplantation, and T-cell depletion in vivo or in vitro [5–7]. Since alternative donor transplantation involving T-cell depletion is increasingly performed [8,9], ADV infection may be of growing impact in adult allo-HSCT.

Treatment strategies include antiviral agents, immune modulation and adoptive immunotherapy. Cidofovir is the most frequently used antiviral drug [10], but has significant nephrotoxicity, and its efficacy in established disease is limited. Tapering or with-

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Table 1
Demographics and treatment characteristics of 399 patients after allogeneic HSCT distributing patients with or without ADV infection.

	All patients (n = 399)	ADV infection (n = 42)	No ADV infection (n = 357)
Median age in years (range)	52 (18–74)	44 (18–74)	53 (18–74)
Donor, n = (%)			
-HLA-matched (8/8 or 10/10)	282 (71)	25 (57)	257 (72)
MRD	94	12	82
MUD	188	13	175
-Alternative; HLA-mismatched (≤ 9/10)	117 (29)	17 (43)	100 (28)
MMURD	50	8	42
Cord blood units	21	4	17
Haploidentical donor:	46	5	41
(TCR/PTCY/cTCR/TCD setting)	(32/14)	(2/3)	(30/11)
≥2nd transplantation, n = (%)	39 (10)	5 (13)	34 (10)
Sex, n = (%)			
Female	177 (44)	17 (40)	160 (45)
Male	222 (56)	25 (60)	197 (55)
Diagnosis, n = (%)			
AML	205 (51)	20 (48)	185 (52)
ALL	53 (13)	5 (12)	48 (13)
Lymphoma	40 (10)	5 (12)	35 (10)
MPN	33 (8)	4 (10)	29 (8)
MM	27 (7)	3 (7)	24 (7)
MDS	23 (6)	2 (5)	21 (6)
SAA	18 (5)	3 (7)	15(4)
Stem cell source, n = (%)			
Peripheral blood stem cells	297 (74)	26 (62)	271 (76)
Bone marrow	67 (17)	9 (21)	58 (16)
Cord blood	21 (5)	4 (10)	17 (5)
Bone marrow followed by peripheral blood stem cells[a]	14 (3)	3 (7)	11 (3)
RIC, n = (%)	332 (83)	32 (76)	300 (84)
ATG therapy, n = (%)	343 (86)	35 (83)	307 (86)
GvHD prophylaxis, n = (%)			
CsA-MMF	225 (56)	16 (38)	209 (59)
CsA-MTX	62 (16)	6 (14)	56 (16)
Cy-MMF-Tacr	31 (8)	2 (5)	29 (8)
Sirolimus-based	31 (8)	8 (19)	23 (6)
others	50 (12)	10 (24)	40 (11)
Acute GvHD, n = (%)			
Grade 0–I	218/387 (56)	16/41 (39)	202/346 (58)
Grade ≥ II	169/387 (44)	25/41 (61)	144/346 (42)
Adenovirus, n = (%)			
Asymptomatic infection	18 (5)	18 (43)	
Localized disease	18 (5)	18 (43)	
Disseminated disease	6 (2)	6 (14)	

Abbreviations: MRD – matched related donor; MUD – matched unrelated donor; MMURD – mismatched unrelated donor; TCR/PTCY –T-cell-replete graft and post-transplantation cyclophosphamide; cTCR/TCD – combined T-cell-replete and T-cell-deplete graft; AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia; MPN – myeloproliferative neoplasm; MM – multiple myeloma; MDS – myelodysplastic syndrome; SAA – severe aplastic anemia; RIC – reduced intensity conditioning; ATG – anti-thymocyte globulin, GvHD – graft-versus-host disease; CsA – cyclosporine A; MMF – mycophenolate mofetil; MTX – methotrexate; Cy – cyclophosphamide; Tacr – Tacrolimus.

[a] Combined T-cell-replete and – deplete haploidentical graft.

drawal of immunosuppression may have a positive impact on outcome of ADV disease [3]. Since the T-cell response is essential for control of viral infection after allo-HSCT [3,11], unselected donor lymphocyte transfusion has been applied [6,12,13], but the safety of this approach is limited by severe GvHD. In contrast, adoptive immunotherapy using selected ADV-specific T cells is a safe and effective treatment of adenovirus disease in children if T cell reconstitution can be achieved [14,15]. Overall, ADV treatment success remains limited, in particular for disseminated disease, and outcome of patients not responding to antiviral agents is poor [5,15].

Here we retrospectively evaluate the occurrence and risk factors of ADV infection in adult recipients of allo-HSCT, with a particular focus on alternative donor transplantation and disseminated disease.

2. Objectives and study design

All adult patients who received allo-HSCT at our institution between January 2007 and December 2011 were evaluated for ADV infection. Data were collected retrospectively, and publication was approved by the local ethics committee. All patients provided informed consent including analysis for scientific purposes.

2.1. Treatment regimens

Patients were treated according to institutional protocols [16–22]. A majority of patients, but no patients undergoing T-cell-replete (TCR) haploidentical transplantation using post-transplantation cyclophosphamide (PTCY), received anti-thymocyte globulin (ATG) for conditioning. No patient received