Annals of Hematology (2018) 97:1209–1217
https://doi.org/10.1007/s00277-018-3290-0

ORIGINAL ARTICLE

Treatment of late-onset hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: the role of corticosteroids

Xiao-Dong Mo[1] · Xiao-Hui Zhang[1] · Lan-Ping Xu[1] · Yu Wang[1] · Chen-Hua Yan[1] · Huan Chen[1] · Yu-Hong Chen[1] · Wei Han[1] · Feng-Rong Wang[1] · Jing-Zhi Wang[1] · Kai-Yan Liu[1] · Xiao-Jun Huang[1,2]

Received: 25 October 2017 / Accepted: 26 February 2018 / Published online: 12 March 2018

Abstract

We aimed to evaluate the treatments, particularly the role of corticosteroids, in patients with late-onset hemorrhagic cystitis (LOHC) after allogeneic hematopoietic stem cell transplantation (allo-HSCT). One hundred and sixty-three consecutive patients who underwent non-T-cell-depleted allo-HSCT and met the criterion of LOHC after allo-HSCT were enrolled in this study. The median time from allo-HSCT to the occurrence of LOHC was 29 (range, 4–155) days. Pathogens identified in blood and/or urine samples from 143 patients were mostly viruses. All of the patients with LOHC received intravenous fluid hydration, alkalization, and forced diuresis, of which 2 patients achieved complete remission (CR) after these treatments. The remaining 161 patients received anti-infection therapies and 71 achieved CR after the therapies. Corticosteroids were additionally applied to 83 out of 90 patients who did not achieve CR after anti-infection therapies, and 88.0% ($n = 73$) of them showed a grade 3 to 4 LOHC at the beginning of corticosteroid therapy. Thirty-five patients showed an immediate response (CR or downgraded at least one grade) within 1 week after the beginning of the corticosteroid therapy. Sixty-four patients (77.1%) achieved CR after corticosteroid therapy, and the median period from the beginning of corticosteroid therapy to CR was 17 days. Thus, we observed that viruses were the most common pathogens in LOHC after allo-HSCT and that anti-infection therapies were critical. For patients not showing a satisfactory response to anti-infection therapies, additional corticosteroid therapy may help to achieve CR.

Keywords Allogeneic hematopoietic stem cell transplantation · Late-onset hemorrhagic cystitis · Corticosteroid · Virus

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for hematological malignancies. Although transplantation techniques have progressed significantly, late-onset hemorrhagic cystitis (LOHC) is still one of the major complications, with an incidence rate varying from 6.5 to 49% [1, 2]. It can cause mortality and lead to a low survival rate [3, 4].

There are several therapeutic methods for LOHC, including ensuring appropriate hydration, hematological homeostasis (maintaining high platelet counts, appropriate red cell counts, and levels of clotting factors), pain relief, catheterization for cystoscopic clot extraction, continuous bladder irrigation with normal saline for prevention of clots and bladder tamponade, anti-infection (particularly antiviral), hyperbaric oxygen, estrogen, clotting factors, and keratinocyte growth factor therapies [5]. Although LOHC tends to be self-limiting after 1 or 2 weeks, some patients, particularly the patients who received alternative donor allo-HSCT, can show refractory LOHC which can persist for several months [6]. Refractory LOHC may lead to poor quality of life, even mortality, after allo-HSCT. Given the assumption that alloimmune injury might also be involved in the pathogenesis of LOHC [7], Huang et al. [8] used corticosteroids to treat patients with refractory LOHC, and all of them achieved complete remission (CR). However, the small sample size of the patients ($n = 11$) in this pilot study limited the ability to further identify the efficacy of corticosteroids in the treatment of LOHC. Thus, in

✉ Xiao-Jun Huang
huangxiaojun@bjmu.edu.cn

[1] Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Peking University Institute of Hematology, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, China

[2] Peking-Tsinghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China

the present retrospective study, we aimed to further evaluate the treatments, particularly the use of corticosteroids, in patients with LOHC after allo-HSCT.

Materials and methods

Patients

A total of 646 consecutive patients underwent non-T-cell-depleted allo-HSCT at the Peking University Institute of Hematology (PUIH) from January 1, 2016, to December 31, 2016: 31, 118, and 497 had undergone human leukocyte antigen (HLA)-unrelated donor (URD) HSCT, HLA-identical sibling donor (ISD) HSCT, and HLA-haploidentical related donor (haplo-RD) HSCT, respectively. One hundred and sixty-three patients who met the criterion of LOHC after allo-HSCT were enrolled in this study: 6, 8, and 149 had undergone URD HSCT, ISD HSCT, and haplo-RD HSCT, respectively (Table 1). The final follow-up visits for the endpoint analysis were conducted on July 31, 2017. Informed consent was obtained from all patients or their guardians, and the study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Peking University People's Hospital.

Transplantation regimen

Preconditioning consisted of cytarabine, busulfan (3.2 mg kg^{-1} day^{-1}, administered intravenously on days − 8 to − 6; day 0 being the first day of donor cell infusion), cyclophosphamide (1.8 g m^{-2} day^{-1}, days − 5 to − 4), and simustine (250 mg m^{-2}, day − 3). Cytarabine was administered at 4 g m^{-2} day^{-1} (days − 10 to − 9) to the haplo-RD group, at 2 g m^{-2} day^{-1} (days − 10 to − 9) to the URD group, and at 2 g m^{-2} day^{-1} (day − 9) to the ISD group. Rabbit antithymocyte globulin (thymoglobulin, 2.5 mg kg^{-1} day^{-1}, days − 5 to − 2; Sanofi, France) was administered to the haplo-RD and URD groups [9, 10]. Granulocyte colony-stimulating factor (G-CSF)-mobilized, fresh, and unmanipulated bone marrow (BM) and peripheral blood harvests were infused into the recipients on the day of collection. In addition, the patients received cyclosporine A (CSA), mycophenolate mofetil (MMF), and short-term methotrexate (MTX) as graft-versus-host disease (GVHD) prophylaxis [11]. Donor selection, HLA typing, and stem cell harvesting were performed as described previously [12, 13]. Minimal residual disease (MRD)-directed immunotherapy (e.g., donor lymphocyte infusion and interferon-α) was given before hematological relapse, as a preemptive intervention therapy, 2 months post-HSCT [14, 15]. Comorbidities in HSCT recipients were assessed by the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) [16].

Table 1 Patient characteristics

Characteristics	LOHC group ($n = 163$)
Median age at HSCT, years (range)	30 (6–61)
Sex, *n* (%)	
Male	102 (62.6)
Female	61 (37.4)
Diagnosis, no. (%)	
AML	57 (35.0)
ALL	68 (41.7)
MDS	14 (8.5)
SAA	12 (7.4)
Others	12 (7.4)
Disease status at transplantation, *n* (%)	
Standard risk	144 (88.3)
High risk	19 (11.7)
Chemotherapy prior to HSCT, *n* (%)	138 (84.7)
Donor–recipient relation, *n* (%)	
Father–child	64 (39.3)
Mother–child	10 (6.1)
Sibling–sibling	47 (28.8)
Child–parent	32 (19.7)
Others	10 (6.1)
Donor type, *n* (%)	
HLA-identical sibling donor	8 (4.9)
HLA-haploidentical related donor	149 (91.4)
HLA-unrelated donor	6 (3.7)
Number of HLA-A, HLA-B, and HLA-DR mismatches, *n* (%)	
0	12 (7.4)
1	2 (1.2)
2	10 (6.1)
3	139 (85.3)
ABO matched	
Matched	80 (49.1)
Major mismatched	39 (23.9)
Minor mismatched	34 (20.9)
Major–minor mismatched	10 (6.1)
HCT-CI before HSCT, *n* (%)	
0	96 (58.9)
1–2	48 (29.4)
≥ 3	19 (11.7)
Median duration of follow-up after HSCT, days (range)	198 (53–410)

AML acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *HLA* human leukocyte antigen, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index, *HSCT* hematopoietic stem cell transplantation, *LOHC* late-onset hemorrhagic cystitis, *MDS* myelodysplastic syndrome, *SAA* severe aplastic anemia

Infection prevention regimen

All of the patients were hospitalized in rooms with high-efficiency particulate-arresting (HEPA) air filters for 4–5 weeks, from day − 10 until the time at which neutrophil recovery was achieved. All of the patients received oral antibiotics (e.g., fluoroquinolone) for gastrointestinal decontamination before and during the period of neutropenia. The patients also received trimethoprim–sulfamethoxazole to prevent *Pneumocystis carinii* infection from days − 10 to + 180, fluconazole or itraconazole capsules for invasive fungal infection from days − 10 to + 75, and acyclovir (200–400 mg) for herpes simplex virus and varicella-zoster virus, administered orally, twice daily, from day + 1 until the time of CSA discontinuation. Ganciclovir (5 mg kg^{-1}) was administered intravenously, twice daily, from days − 9 to − 2, for prophylaxis against cytomegalovirus (CMV) infection. The infection surveillance and treatment protocols used at our institute have been described in detail elsewhere [17].

Detection of pathogens

Blood and urine samples were subjected to real-time polymerase chain reaction (PCR) and reverse transcription-PCR assays for the detection of herpesviruses (herpes simplex virus [HSV] types 1 and 2, Epstein–Barr virus [EBV], CMV, varicella-zoster virus, and human herpesvirus-6 [HHV-6]), respiratory viruses (respiratory syncytial virus [RSV], parainfluenza virus [PIV], influenza types A and B, human metapneumovirus [hMPV], human rhinoviruses [HRVs], human coronaviruses [CoVs; OC43, 229E, NL63, and HKU1], and human bocavirus), polyomaviruses (BK virus and JC virus), adenovirus, parvovirus B19, norovirus, and enterovirus (coxsackievirus and enterovirus 71) [18]. For positive CMV and EBV samples, the pathogen load was determined by quantitative PCR. Additionally, urine samples were subjected to Gram, fungal, and acid-fast bacilli staining, and to bacterial and fungal cultures. These staining and cultures were also performed on blood samples from patients who presented with fever. Blood and urine samples were tested repeatedly weekly.

Definition, prophylaxis, and management of LOHC

Diagnosis of hemorrhagic cystitis (HC) required the presence of sustained hematuria along with dysuria and/or lower abdominal pain. Diagnosis of LOHC required that the symptoms of HC occurred beyond 3 days post-transplantation. The severity of HC was graded according to the published criteria: grade 1, microscopic hematuria on more than two consecutive days; grade 2, macroscopic hematuria; grade 3, macroscopic hematuria with clots; grade 4, macroscopic hematuria with clots and impaired renal function secondary to urinary tract obstruction [1]. Severe LOHC was defined as grade 3 to 4 LOHC, and non-severe LOHC was defined as grade 1 to 2 LOHC.

As prophylaxis for HC, all of the patients were given 3 L m^{-2} day^{-1} of intravenous fluid, from 4 h before to 24 h after the administration of cyclophosphamide. Sodium 2-mercaptoethanesulfonate was given intravenously, at a dose of 15 mg kg^{-1}, prior to cyclophosphamide administration and every 8 h thereafter, over 24 h, until the last dose of cyclophosphamide [19].

With the diagnosis of LOHC, along with the supportive therapies (ensuring appropriate hydration, alkalization, forced diuresis, hematological homeostasis, and pain relief), the patients without GVHD were subjected to tapering of immunosuppressant. The anti-infection therapies included antiviral and antimicrobial therapies. The patients showing CMV-negative blood and urine samples could receive empirical antiviral therapies with 5 mg kg^{-1} day^{-1} of intravenous ganciclovir or 80–120 mg kg^{-1} day^{-1} of intravenous foscarnet sodium [19, 20]. However, the patients showing CMV-positive blood and/or urine samples should receive anti-CMV therapies, i.e., 10 mg kg^{-1} day^{-1} of intravenous ganciclovir or 180 mg kg^{-1} day^{-1} of intravenous foscarnet sodium. The patients with refractory CMV infection, that is, CMV DNAemia lasting for > 2 weeks despite the administration of a full dose of antiviral drug therapy, received the combination of foscarnet and ganciclovir. Antiviral therapies were given for 10–14 days or until 1 week after the virus tests became negative. The patients could also receive empirical antimicrobial therapies, such as carbapenem, cephalosporins containing the β lactamase inhibitor, fourth- or third-generation cephalosporin, or quinolone, for at least 3 days.

For the patients who did not achieve CR after anti-infection therapy, an additional corticosteroid therapy was applied. The dose was prednisone 1 mg kg^{-1} day^{-1}, if the patient's weight was < 50 kg, or prednisone 50 mg day^{-1} for patients whose weight was > 50 kg. Prednisone could be changed by equivalent doses of dexamethasone or methylprednisolone. The patients' response was evaluated 7–10 days later. For the patients responding to corticosteroids, the dose of corticosteroids was reduced, weekly, to two thirds of the dose of the previous week [20]. However, for the patients having other transplant-related complications that also needed corticosteroid therapy during LOHC (e.g., GVHD), the initial time, dosage, and duration of corticosteroid therapy were applied according to these transplanted complications instead of LOHC.

How to manage patients with concurrent active GVHD, CMV infection, and LOHC was critical in the treatment of refractory LOHC in the present study. For the patients having concurrent CMV infection and refractory LOHC, we suggested that systemic corticosteroid therapy could only be considered when the virus was cleared but the LOCH was not CR. However, for the patients having concurrent grade II to IV

acute GVHD and refractory LOHC, systemic corticosteroid therapy should be added immediately with the use of empirical antiviral therapies or anti-CMV therapy (Fig. 1).

The criteria of therapeutic efficiency for LOHC were as follows: (1) CR, HC symptoms were relieved and microscopic hematuria disappeared, and there was no recurrence in the week after achieving CR; (2) partial remission (PR), HC symptoms had significantly improved (such as > 25% reduction in the frequency of urination or relief from dysuria and burning) and/or gross hematuria was downgraded at least one grade, but CR was not achieved; and (3) non-remission (NR), HC symptoms and hematuria did not improve or showed significant deterioration (e.g., gross hematuria upgraded at least one grade).

Definitions and assessments

The patients were classified as "high risk" if they (1) had acute leukemia in its third complete remission (CR3) or greater; (2) had acute leukemia in PR, in NR, or in a state of relapse before HSCT; and (3) had chronic myeloid leukemia after the first chronic phase. All the other patients were stratified into standard-risk categories. Neutrophil engraftment was defined as the first day when the absolute neutrophil count was $\geq 0.5 \times 10^9$ L^{-1} for three consecutive days, and platelet engraftment was defined as the first day when the platelet count was $\geq 20 \times 10^9$ L^{-1} for seven consecutive days without transfusion. GVHD was diagnosed in accordance with the accepted international criteria [21, 22]. Relapse was defined as morphologic evidence of disease in samples from the peripheral blood, bone marrow, or extramedullary sites, or by the recurrence and sustained presence of pre-transplantation chromosomal abnormalities. Patients exhibiting MRD were not classified as showing relapse. Non-relapse mortality (NRM) was defined as death by any cause in the first 28 days post-HSCT or death without evidence of disease recurrence beyond day 28. Overall survival (OS) events were defined as death from any cause. Disease-free survival (DFS) was defined as the survival period with continuous CR.

Statistical analysis

Data were censored at the time of death, relapse, or the last available follow-up. Continuous variables were compared using the Mann–Whitney U test; categorical variables were compared using the χ^2 test and Fisher's exact test. The Kaplan–Meier method was used to estimate the probability of survival. Competing risk analyses were used to calculate the cumulative incidence of LOHC, using Gray's test to evaluate differences between the groups [23]. NRM and relapse were the competing events. The level of significance was set at $P < 0.05$. All reported P values were based on two-sided tests. Data analyses were primarily conducted with SPSS software (SPSS Inc., Chicago, IL, USA), while the R software package (version 2.6.1; http://www.r-project.org) was used for competing risk analysis.

Results

Patient characteristics

Table 1 summarizes the characteristics of the 163 patients with LOHC in this study. Fifteen were children (9.2%) and the other 148 were adults (90.8%). All the patients achieved neutrophil engraftment within 30 days after HSCT, with a median time to neutrophil engraftment of 15 (range, 10–25) days. During the follow-up period, 145 patients exhibited platelet engraftment, with a median time to platelet engraftment of 19 (range, 8–175) days. Six patients showed relapse and 29 died of NRM after HSCT. The 1-year probability of DFS and OS after HSCT was 75.3 and 76.9%, respectively. One hundred

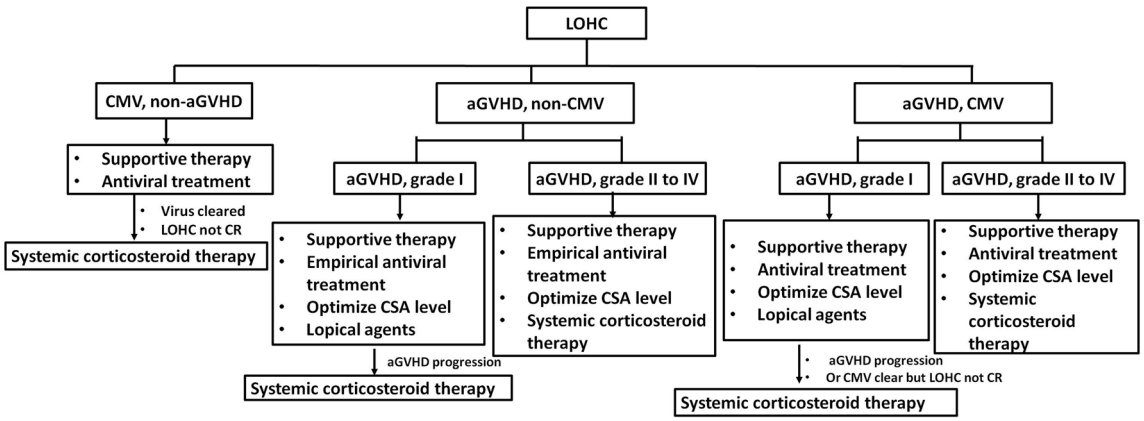

Fig. 1 The management of concurrent active GVHD, CMV infection, and LOHC. For the patients with refractory LOHC only, the dose of systemic corticosteroid therapy was prednisone 1 mg kg^{-1} day^{-1}, for patients whose weight was < 50 kg, or prednisone 50 mg day^{-1} for patients whose weight was > 50 kg. For the patients with grade II to IV acute GVHD, the dose of systemic corticosteroid therapy was methylprednisolone 1 to 2 mg kg^{-1} day^{-1}

and four patients (63.8%) showed acute GVHD, and 15 patients (9.2%) showed grade III to IV acute GVHD.

The median time from transplantation to the occurrence of LOHC was 29 (4–155) days. All the patients exhibited frequent and urgent urination and odynuria. Thirty-four patients exhibited a fever, and the median temperature at LOHC diagnosis was 37.7 (37.3–39.6) °C. The median count of white blood cells, hemoglobin, and platelets on LOHC diagnosis was 4.00 (range, 0.01–30.90) × 10^9 cells L^{-1}, 89 (range, 35–128) g L^{-1}, and 34 (range, 3–194) × 10^9 cells L^{-1}, respectively. Sixteen (9.8%), 53 (32.5%), and 94 (57.7%) patients showed grade 3, 2, and 1 LOHC, respectively, at diagnosis. Ninety-six patients showed progression from the initial grade to a more advanced grade, and 8 (4.9%), 80 (49.1%), 46 (28.2%), and 29 (17.8%) patients showed grade 4, 3, 2, and 1 LOHC, respectively, at peak. The cumulative incidence of LOHC at 100 days after HSCT was 25.1% for the total population and 6.8, 29.8, and 19.4% for ISD HSCT, haplo-HSCT, and URD HSCT recipients ($P < 0.001$; Fig. 2a). The cumulative incidence of grade 3 to 4 LOHC at 100 days after HSCT was 9.0% for the total population and 2.6, 10.9, and 3.2% for ISD HSCT, haplo-HSCT, and URD HSCT recipients, respectively ($P = 0.005$; Fig. 2b).

Pathogens

Pathogens were identified in blood and/or urine samples from 143 patients: 79 had positive blood samples, 13 had positive urine samples, and 51 had simultaneous positive blood and urine samples. Forty-three and 100 patients had infections caused by single and multiple viruses (≥ 2 types of viruses), respectively. In blood samples, CMV was the most common virus (71.8%), followed by BK virus (25.2%), EBV (24.5%), HSV (5.6%), JC virus (5.6%), HHV-6 (4.7%), ADV (2.8%), and PIV (0.9%). In urine samples, the most common virus was BK virus (80.0%), followed by JC virus (21.3%), CMV (4.3%), and ADV (1.3%). The median plasma and urine viral loads of CMV were 1.15 × 10^4/copies (1.00 × 10^3/copies–2.05 × 10^7/copies) and 7.18 × 10^3/copies (7.08 × 10^3/copies–2.48 × 10^4/copies), respectively, and it was identified simultaneously in plasma and urine samples from 2 patients. The median plasma loads of EBV were 4.14 × 10^3/copies (1.00 × 10^3/copies–5.36 × 10^5/copies). BK virus was identified simultaneously in plasma and urine samples from 12 patients, and JC virus was identified simultaneously in plasma and urine samples from 3 patients. The most common bacterium identified in urine samples was *Escherichia coli* ($n = 3$; 1.8%), followed by *Enterococcus faecalis* ($n = 1$; 0.6%), *Proteus mirabilis* ($n = 1$; 0.6%), and *Acinetobacter junii* ($n = 1$; 0.6%).

LOHC therapy

Anti-infection therapies

All patients with LOHC received supportive therapies, and 2 achieved CR after these treatments (grade 1: $n = 1$; grade 2: $n = 1$; no pathogens were detected in blood and urine samples). The remaining 161 patients received anti-infection therapies. All of them received antiviral therapy (72.4% of patients received anti-CMV therapies, and the other 27.6% of patients received empirical antiviral therapies). A total of 138 patients received antibacterial therapies. Seventy-one out of 161 patients (44.1%) achieved CR after anti-infection therapies, and the period from the beginning of anti-infection therapies to CR was 13 (range, 1–50) days. The remaining 90 patients (55.9%) did not achieve CR (NR: $n = 64$; PR: $n = 26$). The rate of CR after anti-infection therapies was

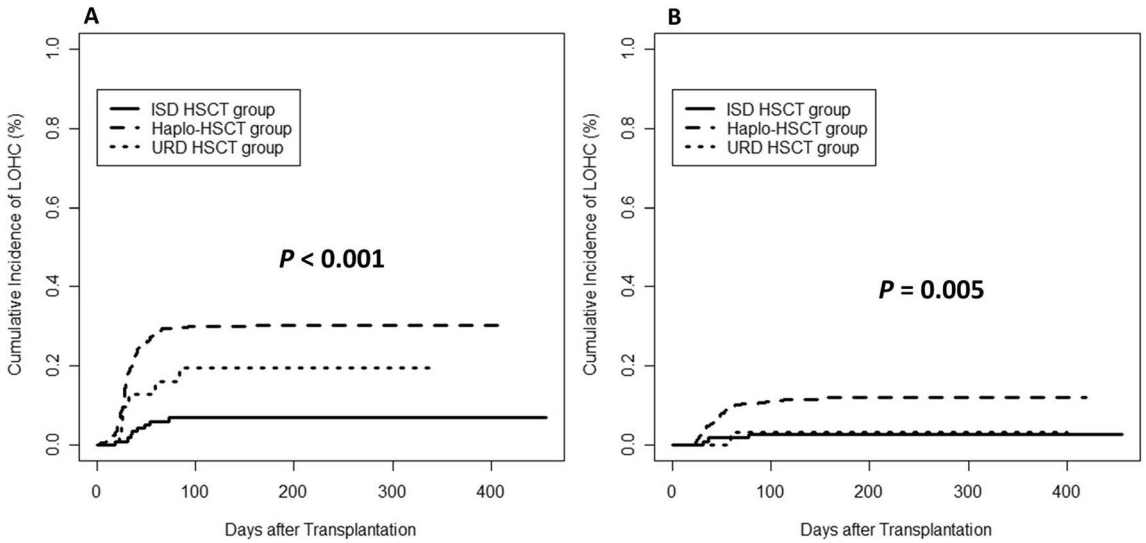

Fig. 2 Cumulative incidence of late-onset hemorrhagic cystitis. The cumulative incidence of total (**a**) and grade 3 to 4 (**b**) late-onset hemorrhagic cystitis according to different donors

significantly lower in the severe LOHC group compared to that of the non-severe LOCH group (12.5 vs. 82.2%, $P < 0.001$).

Corticosteroid therapy

For the 90 patients that did not achieve CR after anti-infection therapies, 7 of them were not subjected to corticosteroid therapy (severe LOHC: $n = 4$; non-severe LOHC: $n = 3$), and none of them achieved CR until the last available follow-up. The other 83 patients received the additional corticosteroid therapy, and 88.0% ($n = 73$) of them showed a severe LOHC at the beginning of corticosteroid therapy. Nine patients showed virus positivity when corticosteroids were administered (CMV: $n = 1$; EBV: $n = 1$; BK virus: $n = 7$). Thirty-three of the patients received corticosteroid therapy because of other transplant-related complications (group A), including GVHD ($n = 26$), engraftment syndrome ($n = 4$), poor graft function ($n = 2$), and diffuse alveolar hemorrhage ($n = 1$). The other 50 patients that received corticosteroid therapy did not have additional transplant-related complications (group B). The median period from the beginning of anti-infection therapies to the beginning of corticosteroid therapy was 10 (range, 0–98) days, which was significantly shorter in group A than that in group B (5 vs. 12 days, $P < 0.001$).

Sixty-nine out of 83 patients (83.1%) responded to corticosteroid therapy (CR: $n = 50$; downgraded at least one grade, although not achieving CR: $n = 19$). Thirty-five out of 69 (50.7%) patients showed an immediate response within 1 week after the beginning of the therapy; particularly, 22 achieved CR within 1 week. For the 19 patients that downgraded at least one grade after therapy, 14 finally achieved CR. Thus, a total of 64 patients (77.1%) achieved CR after corticosteroid therapy. The median period from the beginning of corticosteroid therapy to CR was 17 (range, 0–209) days, which was comparable between groups A and B (18.5 vs. 17 days, $P = 0.444$). In addition, among the other five patients who downgraded at least one grade after corticosteroid therapy, all the symptoms of LOHC were relieved persistently; nevertheless, continuous microscopic hematuria was observed until the last available follow-up.

Among the 90 patients that did not achieve CR after anti-infection therapies, the cumulative incidence of CR for LOHC was significantly higher in the corticosteroid-treated group than that in the corticosteroid non-treated group (79.0 vs. 0.0%, $P = 0.001$; Fig. 3).

Other therapies

For the 14 patients that did not show any response to additional corticosteroid therapy, 1 relapsed and did not receive further therapies for LOHC, and 7 died of NRM (infection: $n = 5$; GVHD: $n = 1$; thrombotic microangiopathy: $n = 1$). For the other 6 patients, 4 were subjected to electrocoagulation hemostasis with cystoscope, and all of them achieved CR after cystoscopy. For the remaining 2 patients, corticosteroid therapy was discontinued, and the patients were subjected to intravenous fluid hydration, alkalization, forced diuresis, continuous bladder irrigation with normal saline, and anti-infection therapies. CR was achieved at the last available follow-up. The treatments of LOHC are summarized in Fig. 4.

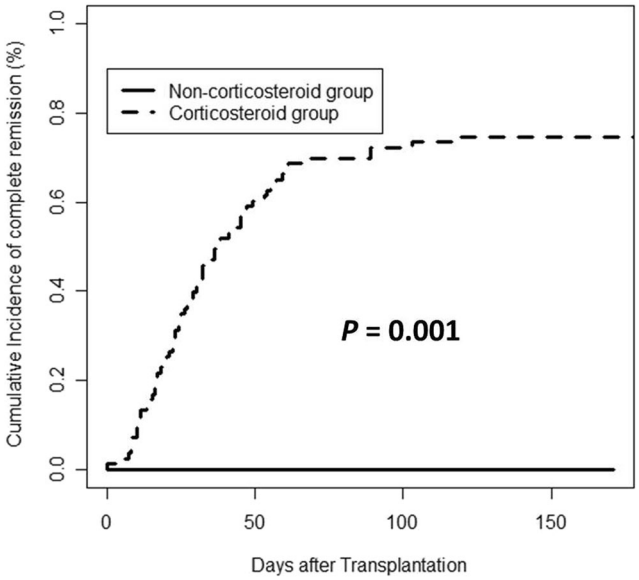

Fig. 3 Response to corticosteroids in patients with late-onset hemorrhagic cystitis showing unsatisfactory response to anti-infection therapies

Discussion

Although transplantation techniques have progressed significantly, LOHC after allo-HSCT continues to seriously influence patients' quality of life. In the present study, we observed that viruses were the most common pathogens in LOHC after allo-HSCT. For patients not showing a satisfactory response to supportive and anti-infection therapies, additional corticosteroid therapy may help to achieve CR. The present study was the largest study identifying the efficacy of corticosteroid therapy in the treatment of LOHC after allo-HSCT.

In the present study, CMV was the most common virus in patients with LOHC. CMV-associated LOHC has been described, as case reports, in some centers [24, 25]. Xu et al. [19] showed that CMV viremia is a risk factor for LOHC (RR = 2.20; 95% CI, 0.9–4.22; $P = 0.08$). Han et al. [26] showed that the cumulative incidence of LOHC at day 100 in patients with and without CMV viremia (prior to or at the onset of LOHC) was 56.3 and 16.7% ($P = 0.018$), respectively, and that CMV viremia (HR = 3.461; 95% CI, 1.005–11.922; $P = 0.049$) was an independent risk factor for the development of LOHC. Thus, decreasing the occurrence of

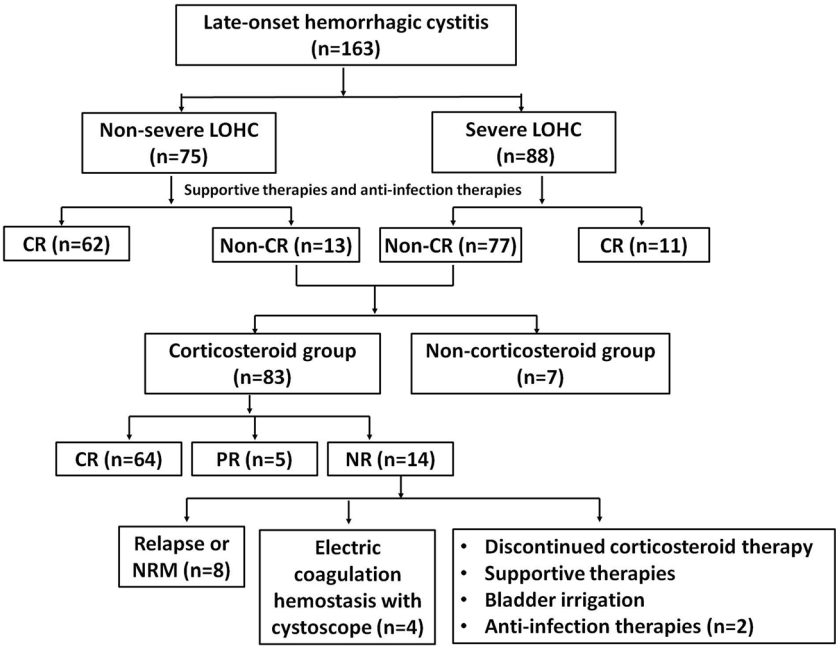

Fig. 4 Treatments for patients with late-onset hemorrhagic cystitis. CR, complete remission; NR, non-remission; NRM, non-relapse mortality; PR, partial remission

CMV viremia is important to decrease the risk of LOHC after allo-HSCT. However, we observed that CMV was identified in urine in only 7 patients, and CMV loads were lower in urine than in plasma. Thus, the role of CMV in LOHC pathogenesis should be further elucidated.

BK virus was another important virus for LOHC, which was the second most common virus in blood samples and the most common virus in urine samples in the present study. Several studies showed that LOHC is strongly associated with the presence of BK virus, although the role of BK virus in LOHC pathogenesis has not yet been fully elucidated [27, 28]. However, we did not detect copies of BK virus, and we could not further identify the association between the burden of BK virus and LOHC.

We observed that pathogens were identified in most patients (143/163) and viruses were the most common pathogens. In addition, many patients (100/143) showed infection with multiple viruses. Previous studies also reported that virus infection was the most important pathogenesis for LOHC [4, 5, 26, 28, 29]. Thus, we hypothesized that anti-infection therapies should be the basis for the treatment of LOHC after allo-HSCT. In the present study, more than 80% of the patients with grade 1 to 2 LOHC achieved CR after anti-infection therapies.

Although infection may be the most important cause of LOHC in allo-HSCT recipients [30], some patients showed unsatisfactory response to anti-infection treatments, particularly for those with severe LOHC. In the present study, only 12.5% of patients with grade 3 to 4 LOHC could achieve CR after anti-infection therapies alone. Thus, other pathogeneses, such as immune injury, may also contribute to the occurrence of LOHC after allo-HSCT. Ost et al. [31] suggested that post-engraftment LOHC represent uroepithelial GVHD. Several studies also reported the association between acute GVHD and LOHC after allo-HSCT [19, 28]. In the present study, we observed that more than 60% of the patients showed acute GVHD. Thus, the association of LOHC with GVHD regarding timing, incidence, and severity suggests that its pathogenesis may involve a local inflammatory environment, cellular immune responses, effector mechanisms, and HLA as well as non-HLA genetics [5]. In addition, several infectious agents can trigger autoimmunity via different mechanisms [32], and several studies have observed that infections, particularly viral infections, can trigger a graft-versus-host reaction [33–35]. In the model of Leung et al. [7] for LOHC, infected uroepithelial cells are attacked by donor lymphoid cells, leading to tissue destruction. Thus, the role of additional corticosteroid therapy after anti-infection and supportive therapies is worth considering in the treatment of patients with LOHC, particularly those showing unsatisfactory responses to anti-infection therapies. Huang et al. [8] reported that 11 patients with refractory LOHC received a low dose of corticosteroids, and all of them achieved CR. In the present study, although 88.0% of the patients who showed an unsatisfactory response to supportive and anti-infection therapies and received additional corticosteroid therapies had severe LOHC, more than half of them showed an immediate response to corticosteroid and 77.1% finally achieved CR. Thus, the additional corticosteroid therapies may be able to significantly shorten and change the course of LOHC and it may be a potential therapy for LOHC patients showing unsatisfactory response to anti-infection therapies.

The present study had several limitations. First, this was a retrospective study, which might have influenced the accuracy

of our findings. Second, we might have underestimated the occurrence of virus-associated LOHC in this study, because the number of viruses that could be tested was relatively small. Third, the several, varied treatments for LOHC introduced heterogeneity into our study results and reduced the reliability of our conclusion about the advantage of corticosteroid therapy for clinical outcomes in patients with LOHC. Future prospective and multicenter studies will provide more information about pathogens and treatments of LOHC after allo-HSCT.

In summary, we observed that viruses were the most common pathogens in LOHC allo-HSCT and that anti-infection therapies were critical for these patients. For patients showing unsatisfactory response to anti-infection therapies, additional corticosteroid therapy may help to achieve CR, particularly for those with severe LOHC.

Acknowledgments The authors thank Editage for their assistance in editing this manuscript and Dr. Yu-Jia Chi, Wei Guo, and Li-Jia Ma for their assistance in collecting the data.

Funding information This work was supported by the Beijing Talents fund (grant number 2015000021223ZK39), the Key Program of the National Natural Science Foundation of China (grant number 81530046), the Foundation for Innovative Research Groups of the National Natural Science Foundation of China (grant number 81621001), the Science and Technology Project of Guangdong Province of China (grant number 2016B030230003), and the Foundation for Nursing Research of the Peking University Health Science Center (grant number BMU20160515).

Compliance with ethical standards

Informed consent was obtained from all patients or their guardians, and the study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Peking University People's Hospital.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Brugieres L, Hartmann O, Travagli JP, Benhamou E, Pico JL, Valteau D, Kalifa C, Patte C, Flamant F, Lemerle J (1989) Hemorrhagic cystitis following high-dose chemotherapy and bone marrow transplantation in children with malignancies: incidence, clinical course, and outcome. J Clin Oncol 7:194–199
2. Russell SJ, Vowels MR, Vale T (1994) Haemorrhagic cystitis in paediatric bone marrow transplant patients: an association with infective agents, GVHD and prior cyclophosphamide. Bone Marrow Transplant 13:533–539
3. Vose JM, Reed EC, Pippert GC, Anderson JR, Bierman PJ, Kessinger A, Spinolo J, Armitage JO (1993) Mesna compared with continuous bladder irrigation as uroprotection during high-dosechemotherapy and transplantation: a randomized trial. J Clin Oncol 11:1306–1310
4. Cesaro S, Facchin C, Tridello G, Messina C, Calore E, Biasolo MA, Pillon M, Varotto S, Brugiolo A, Mengoli C, Palù G (2008) A prospective study of BK-virus-associated haemorrhagic cystitis in paediatric patients undergoing allogeneic haematopoietic stem cell transplantation. Bone Marrow Transplant 41:363–370
5. Harkensee C, Vasdev N, Gennery AR, Willetts IE, Taylor C (2008) Prevention and management of BK-virus associated haemorrhagic cystitis in children following haematopoietic stem cell transplantation—a systematic review and evidence-based guidance for clinical management. Br J Haematol 142:717–731
6. Zheng FM, Fu HX, Han TT, Wang FR, Wang JZ, Chen Y, Yan CH, Zhang YY, Han W, Chen YY, Chen H, Wang Y, Zhang XH, Liu KY, Huang XJ, Xu LP (2017) Comparison of clinical features of hemorrhagic cystitis after haploidentical and matched sibling donor allogeneic hematopoietic stem cell transplantation. Zhonghua Xue Ye Xue Za Zhi 38:656–661
7. Leung AY, Chan MT, Yuen KY, Cheng VC, Chan KH, Wong CL, Liang R, Lie AK, Kwong YL (2005) Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 40:528–537
8. Huang XJ, Liu DH, Xu LP, Zhang HY, Liu KY (2008) Immune-related late-onset hemorrhagic cystitis post allogeneic hematopoietic stem cell transplantation. Chin Med J 121:1766–1769
9. Xiao-Jun H, Lan-Ping X, Kai-Yan L, Dai-Hong L, Yu W, Huan C, Yu-Hong C, Wei H, Jing-Zhi W, Yao C, Xiao-Hui Z, Hong-Xia S, Feng-Rong W, Fei-Fei T (2009) Partially matched related donor transplantation can achieve outcomes comparable with unrelated donor transplantation for patients with hematologic malignancies. Clin Cancer Res 15:4777–4783
10. Wang Y, Liu QF, Xu LP, Liu KY, Zhang XH, Ma X, Fan ZP, Wu DP, Huang XJ (2015) Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study. Blood 125: 3956–3962
11. Huang XJ, Liu DH, Liu KY, Xu LP, Chen H, Han W, Chen YH, Wang JZ, Gao ZY, Zhang YC, Jiang Q, Shi HX, Lu DP (2006) Haploidentical hematopoietic stem cell transplantation without in vitro T cell depletion for the treatment of hematological malignancies. Bone Marrow Transplant 38:291–297
12. Huang XJ, Liu DH, Liu KY, Xu LP, Chen H, Han W, Chen YH, Zhang XH, Lu DP (2009) Treatment of acute leukemia with unmanipulated HLA-mismatched/haploidentical blood and bone marrow transplantation. Biol Blood Marrow Transplant 15:257–265
13. Chang YJ, Luznik L, Fuchs EJ, Huang XJ (2016) How do we choose the best donor for T-cell-replete, HLA-haploidentical transplantation? J Hematol Oncol 9:35
14. Yan CH, Liu DH, Liu KY, Xu LP, Liu YR, Chen H, Han W, Wang Y, Qin YZ, Huang XJ (2012) Risk stratification-directed donor lymphocyte infusion could reduce relapse of standard-risk acute leukemia patients after allogeneic hematopoietic stem cell transplantation. Blood 119:3256–3262
15. Mo XD, Zhang XH, Xu LP, Wang Y, Yan CH, Chen H, Chen YH, Han W, Wang FR, Wang JZ, Liu KY, Huang XJ (2017) Interferon-A is effective for treatment of minimal residual disease in patients with acute leukemia after allogeneic hematopoietic stem cell transplantation: results of a registry study. Biol Blood Marrow Transplant 23:1303–1310
16. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106:2912–2919
17. Mo XD, Zhang XH, Xu LP, Wang Y, Yan CH, Chen H, Chen YH, Han W, Wang FR, Wang JZ, Liu KY, Huang XJ (2016) Late-onset severe pneumonia after allogeneic hematopoietic stem cell transplantation: prognostic factors and treatments. Transpl Infect Dis 18:492–503

18. Li PQ, Zhang J, Muller CP, Chen JX, Yang ZF, Zhang R, Li J, He YS (2008) Development of a multiplex real-time polymerase chain reaction for the detection of influenza virus type A including H5 and H9 subtypes. Diagn Microbiol Infect Dis 61:192–197
19. Xu LP, Zhang HY, Huang XJ, Liu KY, Liu DH, Han W, Chen H, Chen YH, Gao ZY, Zhang YC, Lu DP (2007) Hemorrhagic cystitis following hematopoietic stem cell transplantation: incidence, risk factors and association with CMV reactivation and graft-versus-host disease. Chin Med J 120:1666–1671
20. Fu HX, Xu LP, Liu DH, Liu KY, Chen H, Han W, Zhang XH, Wang Y, Wang FR, Wang JZ, Zhao T, Zhang YY, Chen Y, Huang XJ (2011) Higher proportions of peripheral CD19+CD5+ B cells predict the effect of corticosteroid in patients with late-onset hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation. Chin Med J 124:1517–1523
21. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED (1995) 1994 consensus conference on acute GVHD grading. Bone Marrow Transplant 15:825–828
22. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME (2015) National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 21:389–401
23. Gooley TA, Leisenring W, Crowley J, Storer BE (1999) Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 18:695–706
24. Tutuncuoglu SO, Yanovich S, Ozdemirli M (2005) CMV-induced hemorrhagic cystitis as a complication of peripheral blood stem cell transplantation: case report. Bone Marrow Transplant 36:265–266
25. Bielorai B, Shulman LM, Rechavi G, Toren A (2001) CMV reactivation induced BK virus-associated late onset hemorrhagic cystitis after peripheral blood stem cell transplantation. Bone Marrow Transplant 28:613–614
26. Han TT, Xu LP, Liu DH, Liu KY, Fu HX, Zhao XY, Zhao XS, Huang XJ (2014) Cytomegalovirus is a potential risk factor for late-onset hemorrhagic cystitis following allogeneic hematopoietic stem cell transplantation. Am J Hematol 89:55–61
27. Satyanarayana G, Marty FM, Tan CS (2014) The polyomavirus puzzle: is host immune response beneficial in controlling BK virus after adult hematopoietic cell transplantion? Transpl Infect Dis 16:521–531
28. Leung AY, Yuen KY, Kwong YL (2005) Polyoma BK virus and haemorrhagic cystitis in haematopoietic stem cell transplantation: a changing paradigm. Bone Marrow Transplant 36:929–937
29. Uhm J, Hamad N, Michelis FV, Shanavas M, Kuruvilla J, Gupta V, Lipton JH, Messner HA, Seftel M, Kim DD (2014) The risk of polyomavirus BK-associated hemorrhagic cystitis after allogeneic hematopoietic SCT is associated with myeloablative conditioning, CMV viremia and severe acute GVHD. Bone Marrow Transplant 49:1528–1534
30. Gorczynska E, Turkiewicz D, Rybka K, Toporski J, Kalwak K, Dyla A, Szczyra Z, Chybicka A (2005) Incidence, clinical outcome, and management of virus-induced hemorrhagic cystitis in children and adolescents after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 11:797–804
31. Ost L, Lönnqvist B, Eriksson L, Ljungman P, Ringdén O (1987) Hemorrhagic cystitis—a manifestation of graft versus host disease? Bone Marrow Transplant 2:19–25
32. Sener AG, Afsar I (2012) Infection and autoimmune disease. Rheumatol Int 32:3331–3338
33. Gammon B, Cotliar J (2013) Viral infection as a trigger in flares of acute graft-versus-host disease. Br J Dermatol 168:906–908
34. Kawano N, Gondo H, Kamimura T, Aoki K, Iino T, Ishikawa F, Miyamoto T, Nagafuji K, Shimoda K, Hayashi S, Otsuka T, Kazuyama Y, Harada M (2003) Chronic graft-versus-host disease following varicella-zoster virus infection in allogeneic stem cell transplant recipients. Int J Hematol 78:370–373
35. Pichereau C, Desseaux K, Janin A, Scieux C, Peffault de Latour R, Xhaard A, Robin M, Ribaud P, Agbalika F, Chevret S, Socié G (2012) The complex relationship between human herpesvirus 6 and acute graft-versus-host disease. Biol Blood Marrow Transplant 18:141–144