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Clinical study of late-onset hemorrhagic cystitis after allo-HSCT without in vitro T-cell depletion

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Abstract

This study is to investigate the hemorrhagic cystitis (HC) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) without in vitro T-cell depletion. Patients receiving allo-HSCT in 2019 were enrolled. The occurrence and clinical characteristics of HC after HLA-identical HSCT and haploidentical HSCT were retrospectively analyzed. BK, JC, cytomegalovirus, and other viruses were monitored when HC occurred. Conventional HC treatment was performed. Additionally, 5 cases of severe refractory HC were treated with adipose-derived mesenchymal stem cell (ADSC) besides conventional HC treatment. Totally, 54 patients with allo-HSCT were enrolled, including 12 cases with HLA-identical HSCT and 42 cases with haploidentical HSCT. Among them, 17 developed late-onset HC (LOHC). There was no early-onset HC. The median onset time was 33.5 (9–189) days, with a median duration of 19 (5–143) days. There were 8 cases of grade III HC and 2 cases of grade IV HC. The cumulative incidence of LOHC in 54 patients was 29.6%, and the cumulative incidence of LOHC in 42 patients with haploidentical HSCT was 40.5%. The 1-year expected progression-free survival (PFS) of 26 patients without HC was 86.6%, and the 1-year expected PFS of 16 HC patients was 74.5%. However, there was no statistically significant difference (P = .326). The urine BK virus of 14 patients was positive, with the lowest of 1.98×10^5 copies/mL, and the highest of 8.96×10^5 copies/mL. For the 5 patients with severe refractory HC, the lowest infusion dose of ADSC was 0.9×10^6/kg and the highest was 1.4×10^6/kg. All 5 patients were cured. The incidence of LOHC is higher after haploidentical HSCT. LOHC is positively correlated with urine BK virus. LOHC has no obvious effect on the overall PFS of patients. ADSC infusion has a good therapeutic effect on severe and prolonged LOHC.

Abbreviations: ADSC = adipose-derived mesenchymal stem cell, aGVHD = acute graft-versus-host disease, allo-HSCT = allogeneic hematopoietic stem cell transplantation, ATG = antithymocyte globulin, Bu = Busulfan, CMV = cytomegalovirus, Cy = cyclophosphamide, Haplo-RD = haploidentical related donor, HC = hemorrhagic cystitis, ISD = identical sibling donor, LOHC = late-onset HC, MAC = myeloablative conditioning, MSCs = mesenchymal stem cells, PFS = progression-free survival, RIC = reduced intensity conditioning, SAA = severe aplastic anemia.

Keywords: adipose-derived mesenchymal stem cells, allogene hematopoietic stem cell transplantation (allo-HSCT), BK virus, hemorrhagic cystitis (HC), T-cell depletion

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been currently recognized as 1 of the effective treatments for hematological malignancies. Hemorrhagic cystitis (HC), 1 of the common and serious complications of allo-HSCT, is clinically characterized by hematuria and other bladder irritation symptoms including frequent urination, urination urgency, and painful urination. HC is defined as, starting from pretreatment, the continuous presence of hematuria based on microscopic or gross observation for 7 days or above, in the absence of bleeding, diffusive intravascular coagulation, multiple organ dysfunction syndrome, or sepsis caused by menstruation and/or other gynecological diseases.

According to the occurrence time, HC can be divided into the early-onset HC (occurring within 28 to 72 hours of conditioning regimen) and late-onset HC (LOHC; occurring at more than 72 hours after conditioning regimen). It has been shown that, the incidence of HC is 7% to 68%, while the incidence of severe HC is 29% to 44%.[1–3] Severe HC seriously affects the quality of life of patients' after transplantation, and also increases the mental and economic burden of patients.

HY and GC contributed equally to this work.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (approval no.: 20180622-10). Informed consent was obtained from each patient.

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In this cross-sectional study, the patients receiving allo-HSCT in 2019 in our Transplant Center were included, and the occurrence and treatment of HC were analyzed. The cumulative occurrence of HC, the relationship with BK virus, the impact on progression-free survival (PFS) after transplantation, and the treatment of severe HC by ADSCs were investigated.

2. Materials and Methods

2.1. Study participants

Totally, 54 patients receiving allo-HSCT in 2019 in our Transplant Center were included in this study. There were 31 males and 23 females, with a median age of 37.5 years (ranging from 4 to 61 years). Among these patients, there were 30 cases of acute myeloid leukemia, 13 cases of acute lymphoblastic, 6 cases of severe aplastic anemia (SAA), 2 cases of myelodysplastic syndrome, 2 cases of chronic myelogenous leukemia, and 1 case of primary mucopolysaccharidosis. Moreover, among these patients, there were 12 cases of HLA-identical sibling donor (ISD) HSCT (9 cases of myeloablative conditioning (MAC) and 3 cases of reduced intensity conditioning (RIC)), and 42 cases of haploidentical related donor (Haplo-RD) HSCT (33 cases of MAC and 9 cases of RIC) (Table 1). The follow-up ended on May 31, 2020. All patients had engraftment and complete hematopoietic reconstruction. Informed consent was obtained from each patient. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (approval no.: 20180622-10).

2.2. Transplantation regimen

1. MAC regimen: Cytarabine was administered at 2 to 4 $g \cdot m^{-2} \cdot day^{-1}$ (day −9 to day −8), Busulfan (Bu) was administered at 3.2 $mg \cdot kg^{-1} \cdot day^{-1}$ (day −7 to day −5), and cyclophosphamide (Cy) was administered 1.8 $g \cdot m^{-2} \cdot day^{-1}$ (day −3 to day −2). Rabbit antithymocyte globulin (rATG; 2.5 $mg \cdot kg^{-1} \cdot day^{-1}$, from day −4 to day −1) was administered to the Haplo-RD patients.

2 . Conditioning regimen for SAA patients.

F + Bu + Cy + ATG regimen for ISD patients: fludarabine, 30 $mg \cdot m^{-2} \cdot day^{-1}$ (day −9 to day −5); Bu, 3.2 $mg \cdot kg^{-1} \cdot day^{-1}$ (day −6 to day −5); Cy, 50 $mg \cdot kg^{-1} \cdot day^{-1}$ (day −3 to day −2); rATG, 2.5 $mg \cdot kg^{-1} \cdot day^{-1}$ (day −4 to day −1).

Bu + Cy + ATG regimen for Haplo-RD patients: Bu, 3.2 $mg \cdot kg^{-1} \cdot day^{-1}$ (day −7 to day −6); Cy, 50 $mg \cdot kg^{-1} \cdot day^{-1}$ (day −5 to day −2); rATG, 2.5 $mg \cdot kg^{-1} \cdot day^{-1}$ (day −5 to day −2).

3. RIC regimen: fludarabine, 30 $mg \cdot m^{-2} \cdot day^{-1}$ (day −9 to day −5); Cytarabine, 2 $g \cdot m^{-2} \cdot day^{-1}$ (day −9 to day −5); Bu, 3.2 $mg \cdot kg^{-1} \cdot day^{-1}$ (day −4 to day −3). The rATG (2.5 $mg \cdot kg^{-1} \cdot day^{-1}$, day −4 to day −1) was administered to the Haplo-RD RIC patients.

2.3. Prevention of GVHD

The prevention of GVHD was based on the CsA or Tac + short-term MTX + MMF + Glu, CSA Day −5 to Day + 100, with the initial dosage of 2 to 2.5 mg/kg/day intravenous drip, 4 to 5 mg/kg/day oral administration, or Tac, Day −5 to Day + 100, with the initial dosage of 0.02 mg/kg/day intravenous drip, 0.05 mg/kg/day oral administration in 2 doses; MMF, 0.5 b.i.d p.o, for the Haplo-RD patients, Day −1 to Day + 100, and for the ISD patients, Day −1 to Day + 30; MTX, 15 mg/m^2/day Day + 1, and 10 mg/m^2/day, Days + 3, +6, and + 11, ivgtt; the Haplo-RD patients was treated with anti-CD25 monoclonal antibody (12 mg/m^2), 20 mg ivgtt q.d, Days + 1 and + 2; the patients with haploidentical HSCT received dexamethasone, 2.5 mg iv q12h, Day + 1 to Day + 15 after transplantation, which was gradually changed to oral administration of prednisone, till withdrawal.

2.4. Stem cell source

The source of stem cells in SAA patients was bone marrow mobilized by G-CSF plus peripheral blood, and the source for the rest of patients was the peripheral blood mobilized by G-CSF.

2.5. Virus prevention

The ganciclovir injection was given on day −7 to day −1: 250 mg ivgtt b.i.d, which was changed into acyclovir injection on day + 1, 250 mg ivgtt b.i.d. After the neutrophils were more

Table 1

Patient, donor, and graft characteristics.

Variable	HLA-identical sibling donor HSCT (n = 12)	Haploidentical related donor HSCT (n = 42)
Median age, year (range)	38(21–61)	30(4–61)
Age 0 to 20 year, n (%)	0(0)	11(27)
Age 21 to 35 year, n (%)	5(42)	9(21)
Age older than 35 year, n (%)	7(58)	22(52)
Disease, n (%)		
AML	6(50)	24(57)
ALL	4(34)	9(22)
SAA	1(8)	5(12)
MDS	1(8)	1(2)
CML	0(0)	2(5)
Other	0(0)	1(2)
Disease status, n (%)		
Standard	1(8)	0(0)
Intermediate	0(0)	5(12)
Advanced	10(84)	34(81)
Other	1(8)	3(7)
Donor-patient sex match, n (%)		
Male-Male	5(41)	12(29)
Male-Female	2(17)	11(26)
Female-Male	3(25)	11(26)
Female-Female	2(17)	8(19)
ABO match, n (%)		
Matched	9(75)	26(62)
Minor mismatched	0(0)	10(24)
Major mismatched	1(8)	6(14)
Absolute mismatched	2(17)	0(0)
Donor-patient relationship, n (%)		
Mother to child	0(0)	7(17)
Father to child	0(0)	8(19)
Child to patient	0(0)	14(33)
Sibling	12(100)	13(31)
Graft type, n (%)		
Bone marrow + peripheral blood	1(8)	5(12)
Peripheral blood alone	11(92)	37(88)
Median mononuclear cells, $\times 10^8$/kg (range)	10.12(7.8–14.2)	12.9(7.4–20)
Median $CD34^+$ count, $\times 10^6$/kg (range)	6.55(4.6–8.7)	7.6(4.8–11.4)

ALL = acute lymphoblastic, AML = acute myeloid leukemia, CML = chronic myelogenous leukemia, HSCT = hematopoietic stem cell transplantation, MDS = myelodysplastic syndrome, SAA = severe aplastic anemia.

than 0.5×10^9/L, the injection was changed to ganciclovir injection on day + 15, according to blood routine application for 2 consecutive weeks.

2.6. HC classification and prevention

For the HC classification, the cases with microscopic hematuria were classified as grade I, gross hematuria as grade II, gross hematuria with blood clot as grade III, and gross hematuria and blood clot complicated with urethral obstruction as grade IV. Grades I-II were mild, while grades III-IV were severe.[4–6]

For the prevention of HC, during the Cy application, a large amount of uniform fluid replacement was given for 24 hours, and Mesna (sodium thioethanesulfonate) was used to prevent hemorrhagic cystitis. For the high-dose rehydration, the total daily fluid volume was calculated at 100 to 120 mL/kg/day, through a uniform intravenous drip continuing for 24 hours. To alkalinize the urine, sodium bicarbonate dosage was 0.5% of the total rehydration volume. To achieve diuresis, the furosemide injection was given, 20 mg each time, once every 6 hours, while the potassium was supplemented. The dosage of Mesna was 1.2 times that of CTX, with the initial dosage of 20% of CTX, which was applied simultaneously with CTX, and the rest of Mesna was maintained for 24 hours through intravenous drip.

2.7. Examinations and virus detection for HC

The patients developing HC were subjected to the urinary tract ultrasound, gynecological ultrasound (for females), multiple urine routine tests, urinary bacteria and fungi cultures, and cystoscopy if necessary. Moreover, the patients developing HC also received the detection of the blood cytomegalovirus (CMV) antibody and DNA, blood BK and JC virus, and the PCR detection for urine CMV, BK and JC viruses. Meanwhile, blood and urine BK and JC viruses were tested for patients without HC during the same period.

2.8. General treatment of HC

Once diagnosed, the patients received a large dose of fluids immediately (the daily fluid volume should be calculated at 100 to 120 mL/kg), and the intravenous injection continued for 24 hours. Meanwhile, the sodium bicarbonate would also be given, combined with treatment with furosemide and diuresis, together with the empirical application of the ribavirin or acyclovir antiviral therapy.

2.9. Adipose-derived mesenchymal stem cell (ADSC) treatment for severe HC

For the patients with severe HC, if no improvement was achieved after more than 1 month of comprehensive treatments (such as antiviral therapy, rehydration, and diuresis), the ADSCs were then used as the adjuvant therapy. ADSCs were obtained from the healthy third parties. Hailong Yuan, the project leader, provided the source of ADSCs and was proven as a healthy donor, who was subjected to the detections on hepatitis immunity, CMV, Epstein-Barr virus, and AIDS in the First Affiliated Hospital of Xinjiang Medical University (Photos, videos and testimonials were available for these medical examinations). ADSC preparation was performed by the Beijing Health & Biotech Co, Ltd (Beijing, China). A framework agreement with our hospital has been signed, confirming the company's qualification according to the Office of Translational Medicine and the Medical Affairs Department.

The dosage of ADSC was 1×10^6/kg for each infusion (once a week), following intravenous injection with 5 mg dexamethasone. During the ADSC infusion, the patient's blood pressure, heart rate, respiration, body temperature, and with or without chilling and/or dyspnea, were closely monitored, and the patient's subjective symptoms were also recorded. After 2, 4, 8, 12 hand 24 hours, respectively, the urine samples were obtained. The patient received the urine routine test every day, and the patient's symptoms and signs were recorded in details. The hepatitis B, hepatitis C, humoral immunity, CMV-DNA, Epstein-Barr virus, as well as the blood and urine BK and JC viruses were checked every 2 weeks, until 1 month after ADSC treatment. After 3 infusions of ADSCs, if there was still no significant improvement in the assessment of symptoms, the infusion would be stopped.

2.10. Therapeutic efficiency evaluation

The therapeutic efficiencies for HC were evaluated as follows: curative: frequent urination, urgency and dysuria symptoms disappeared; the urine routine tests showed no abnormalities for 7 consecutive days; significantly effective: severe HC was changed into mild HC (levels I-II); effective: frequent urination, urgency, pain and other symptoms were relieved, the urine red blood cell count was decreased by more than 50%, and the grade IV HC was changed into grade III; and ineffective: the patient's symptoms and laboratory tests showed no improvement.

2.11. Statistical analysis

The SPSS25.0 statistical software was used for statistical analysis. The *t*-test was used for the comparison of the ages between these 2 groups, and the χ^2 test was used for the comparison of gender and disease types. Cumulative incidence of HC was analyzed by the Kaplan-Merier survival analysis and the *Log-rank* test.

3. Results

3.1. Analysis of HC incidences

In these 54 patients with allo-HSCT, 17 (11 females and 6 males) developed late-onset HC, while no early-onset HC case was reported. The baseline information for the 17 patients with HC is presented in Table 2. All of these cases were with haploidentical HSCT, while no HC was reported in the patients with HLA-identical HSCT. The median onset time was 33.5 days (from 9 to 189 days) after transplantation, with the median duration of 19 days (from 5 to 143 days). There were 1 case of grade I, 6 cases of grade II, 8 cases of grade III, and 2 cases of grade IV. For these 54 patients, the accumulated LOHC incidence was 29.6% (95% CI, 17.5%–41.7%), and the cumulative incidence of LOHC in the 42 patients with haploidentical HSCT was 40.5% (95% CI, 25.6%–55.4%) (Figs. 1 and 2).

Among these 42 patients with haploidentical HSCT, 33 cases were pretreated with MAC, 15 cases developed HC, and 6 cases developed severe HC, with the LOHC cumulative incidence of 45.5% (95% CI, 28.45%–62.55%). On the other hand, 9 cases were pretreated with RIC, and 2 cases developed HC (all severe HC cases), with the LOHC cumulative incidence of 23% (95% CI, 7.72%–38.28%). The cumulative incidence of LOHC in MAC patients was higher than that in RIC patients, with however no statistically significant differences ($P > .05$) (Fig. 3).

3.2. Analysis of HC and survival

Till the end of the follow-up period at May 2020, the 1-year expected PFS of 26 patients without HC was 86.6% (95% CI, 76.8%–96.4%), and the 1-year expected PFS of 16 HC patients was 74.5% (95% CI, 56.9%–92.1%). PFS for patients without

Table 2

The baseline information of the 17 patients with HC.

No.	Diagnosis	Age (year)	Sex
1	AML	41	Female
2	ALL	24	Male
3	AML	23	Female
4	ALL	22	Female
5	ALL	19	Male
6	AML	38	Female
7	MDS	46	Female
8	MDS	42	Female
9	ALL	35	Female
10	ALL	18	Female
11	ALL	17	Male
12	ALL	14	Male
13	MDS	29	Male
14	AML	43	Female
15	ALL	37	Female
16	AML	16	Female
17	AML	33	Male

ALL = acute lymphoblastic, AML = acute myeloid leukemia, HC = hemorrhagic cystitis, MDS = myelodysplastic syndrome.

HC was higher than that of the HC patients, with however no statistically significant differences ($P = .326$) (Fig. 4).

3.3. Analysis of HC and virus infection

Totally, 17 HC patients were negative for CMV in blood and urine, and negative for the Epstein-Barr virus. One patient was positive for BK-DNA in blood, and the remaining 15 patients were negative for BK-DNA. Moreover, 14 patients were positive for BK virus in the urine, with a minimum of 1.98×10^5 copies/mL and a maximum of 8.96×10^5 copies/mL. Furthermore, 2 patients were negative for BK and JC viruses in the blood and urine. Two patients were positive for BK and JC viruses in the urine. The occurrence of HC was positively correlated with urine BK virus.

3.4. Corticosteroid treatment for severe HC

Totally, 4 patients received the corticosteroid treatment. Our results showed that 1 patient was negative for the tests of related viruses. After the failure of conventional treatment, methylprednisolone was administered intravenously without obvious infection, and the symptoms improved significantly after 3 days. Moreover, 3 patients had acute graft-versus-host disease (aGVHD) before HC occurrence or when HC occurred. After BK virus became negative, if the patients still had symptoms, they were given methylprednisolone intravenous treatment for 3 to 5 days. These patients were subsequently cured.

3.5. ADSC treatment for severe HC

Among the 17 HC patients, 5 patients had delayed symptoms for 1 month due to the disease course, and then the ADSC treatment was performed (Table 3). The planned dose of each infusion was 1×10^6/kg, and the actual infusion dose for the patients ranged from 0.9×10^6/kg to 1.4×10^6/kg. All 5 patients were cured, showing therapeutic effectiveness after 3 injections. For the second patient, the HC lasted for 120 days, who received the hemostasis treatment under cystoscope and the visceral artery embolization for the bilateral internal iliac arteries, which did not achieve sustained clinical efficacy. When ADSC was infused for 3 times, the therapeutic efficacy was evaluated as effective, and the efficacy was evaluated as markedly effective at 1 week after the fifth infusion. The second patient was cured after 2 weeks. For the third patient, the HC duration lasted for 143 days, which was the longest duration. The patient received continuous treatment for the bladder irrigation and the hemostasis treatment under cystoscope, which did not achieve sustained clinical efficacy. After 3 infusions of ADSCs, the efficacy was evaluated as effective, after the fifth infusion, the efficacy was evaluated as markedly effective.

4. Discussion

HC is a common complication after allo-HSCT. Lu et al[7] have shown that the occurrence of HC during Haplo-RD HSCT was significantly higher than that of ISD HSCT. ATG has been considered to be related to the occurrence of HC. Kerbauy et al[8] have shown that the using ATG in conditioning regimen would significantly increase the incidence of HC associated with the BK virus infection. In this study, the HC patients were all Haplo-RD HSCT patients, also suggesting that ATG represented an independent pathogenic factor of HC. Salem et al[9] have shown that in the haploidentical HSCT with fludarabine in conditioning regimen, the incidence of BK virus-related HC in the ATG 7.5 mg/kg group was higher than that of the ATG 6 mg/kg group (15% and 3%, respectively). In this study, 10 mg/kg ATG was applied. However, whether different doses of ATG can affect the occurrence of HC remain to be studied.

Viral infection has been generally considered to be the main cause of HC. It has been shown that the ADV infection is a major cause of LOHC after allo-HSCT.[10,11] Moreover, the occurrence of LOHC is related to CMV and influenza virus.[12,13] Arthur et al[14] have described the relationship between HC and BK virus after bone marrow transplantation for the first time, and most of the serum samples from adults were positive for the BK virus, a member of polyoma virus. In allo-HSCT, the chemotherapy in conditioning regimen would cause damages to the urothelium, prolong the duration of immunosuppression, cause virus replication and shedding, induce inflammation and damages to the bladder mucosa, and ultimately lead to hematuria, pain and other uncomfortable symptoms. BK virus has been generally considered to be 1 of the main causes of HC, and the occurrence of about 4% to 50% HC cases is related to BK virus.[8,14–19] In this study, our results showed that BK virus is the main causes of HC occurrence. Almost all the HC patients had positive BK virus in the urine with a high virus copy number, but no significant correlation between the copy number and the HC severity was found. There seemed to be no obvious correlation between the JC virus and the HC occurrence. Almost no BK or JC was detected in the blood samples from the HC patients, suggesting that blood BK and JC detection may not have clinical significance for the diagnosis of HC. In recent years, studies have shown that BK virus would increase the risk of treatment-related mortality, but only had limited impact on overall survival after transplantation.[19–21] In this study, our results showed that HC did not increase treatment-related mortality and exerted no significant effect on PFS. Retrospective and prospective investigations with larger sample sizes are still needed to address these issues in the future.

Mesenchymal stem cells (MSCs) represent a type of adult pluripotent stem cells with multiple differentiation potentials.[22] MSCs play a role in promoting tissue repair through the following 2 pathways[23]: directly participating in tissue damage repair under local microenvironments; and indirectly participating in tissue damage repair by secreting a variety of cytokines and cell growth factors to improve the microenvironment at the tissue damage site. MSCs have low immunogenicity and have immunomodulatory effects.[24–26] Therefore, in recent years, there have been more and more studies using MSCs to treat HC. Ringden et al[27] have reported 12 cases of HC patients after HSCT, and they have shown that, after intravenous infusion of MSC, hematuria completely disappeared

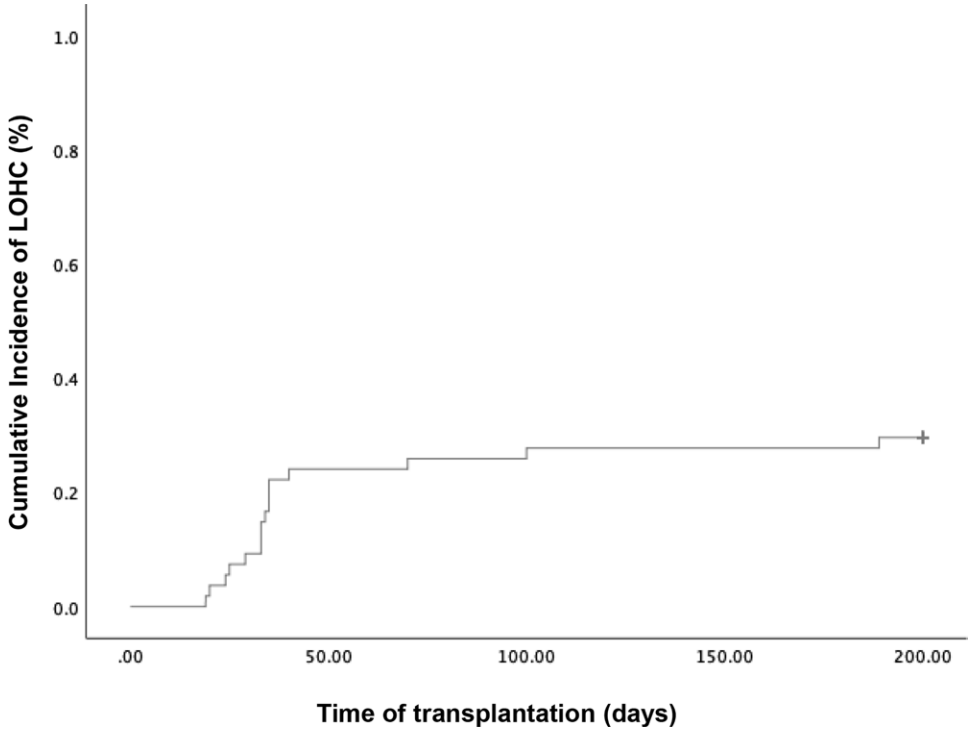

Figure 1. Cumulative incidence of LOHC in 54 patients. LOHC = late-onset hemorrhagic cystitis.

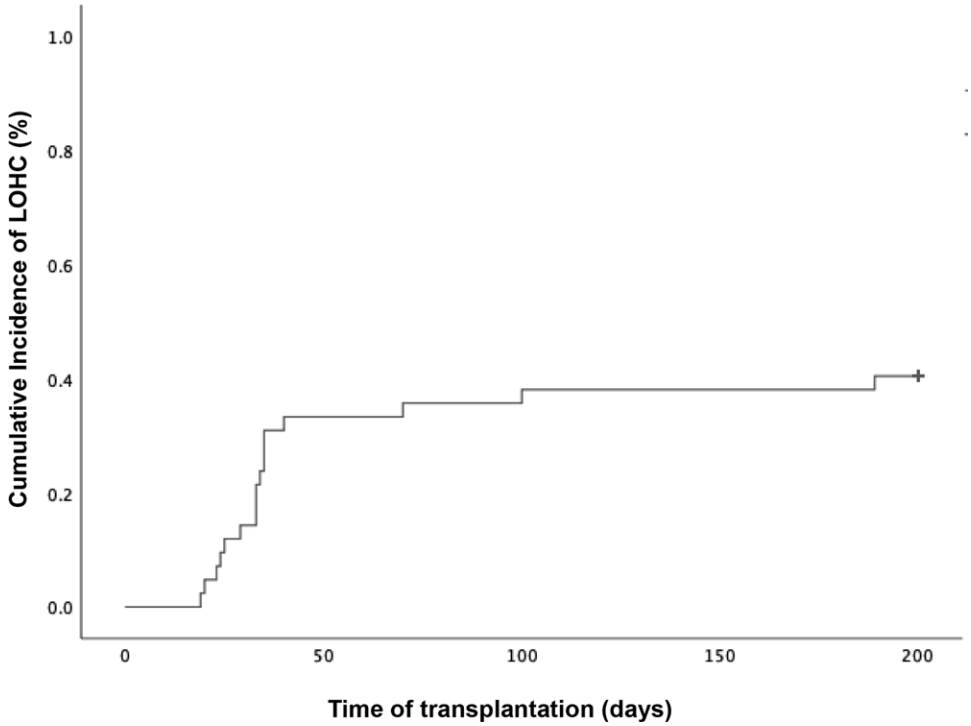

Figure 2. Cumulative incidence of LOHC in 42 haploidentical patients. LOHC = late-onset hemorrhagic cystitis.

in 8 cases, but not in the other 2 cases. However, the blood transfusion volume was significantly reduced. It is worth noting that, 1 patient obtained MSCs from 2 donors in succession, and DNAs were found during autopsy from these 2 donors in the patient's bladder tissue, further confirming that the MSCs have homing effects. Baygan et al[28] have treated 11 patients with HC after HSCT using MSCs, and the average disappearance time of hematuria was 22 days. The hematuria mainly last for 42 days in HC patients of grade 3 and above without MSCs treatment, suggesting that MSCs may be a feasible new treatment option for HC. Moreover, in a previous study from Wang et al,[29] 7 out of 33 HC patients were treated with MSCs, for at least 1 MSCs infusion, with 6 patients receiving MSCs infusion within 3 days of the beginning of hematuria and 1 case receiving MSCs infusion at 40 days after the beginning of hematuria. Among these patients, 3 patients reported significant efficacy,

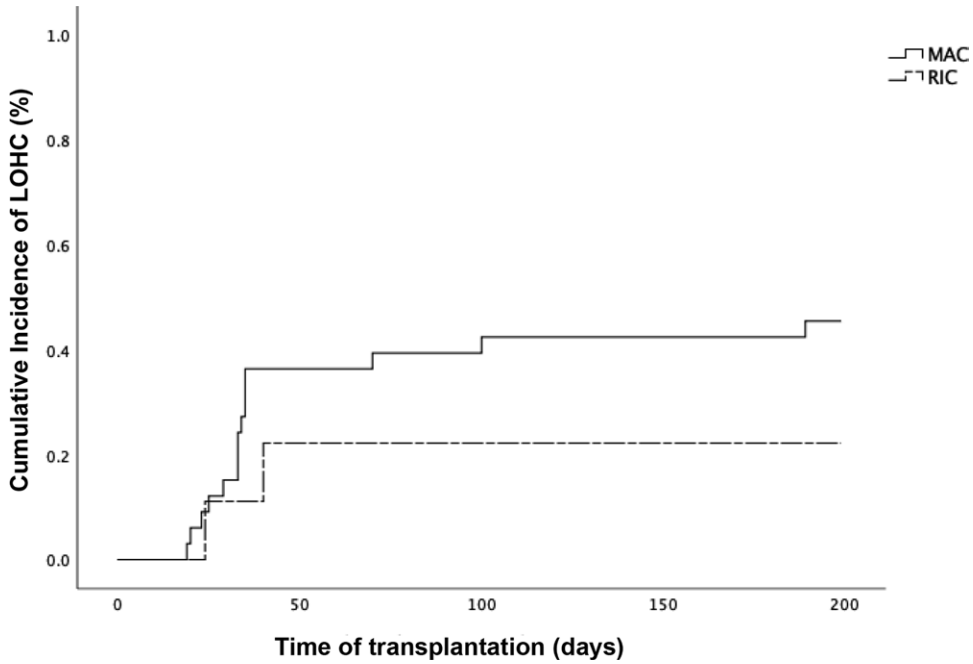

Figure 3. Cumulative incidence of LOHC in 33 MAC and 9 RIC patients. LOHC = late-onset hemorrhagic cystitis, MAC = myeloablative conditioning, RIC = reduced intensity conditioning.

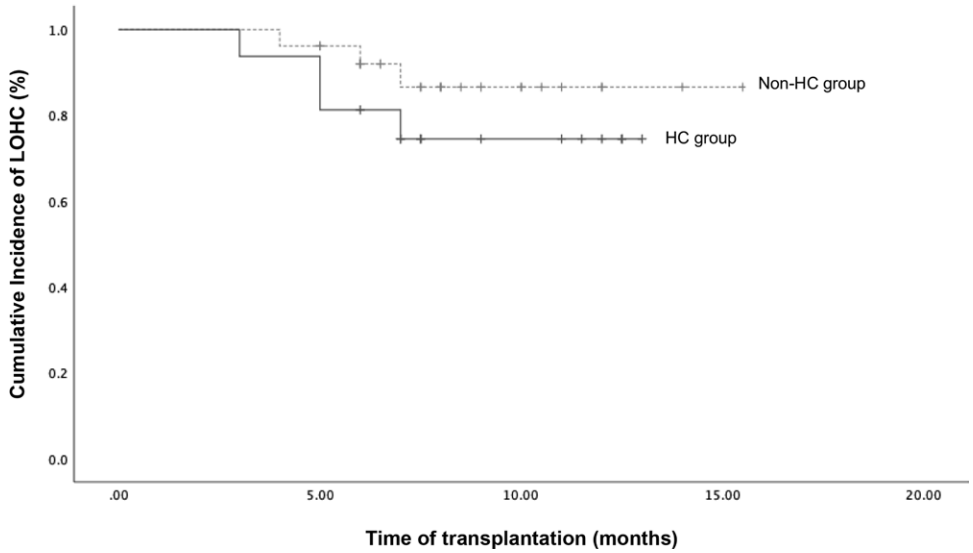

Figure 4. Cumulative incidence of PFS in 26 non-HC patients and 16 HC patients. HC = hemorrhagic cystitis, PFS = progression-free survival.

Table 3

Clinical information of the 5 cases with severe HC.

Case	Onset time (years old)	HC grade	Virus	ADSC infusion, n × 10^6/kg	Times of infusions	Outcome
1	30	III	BK virus	1.0	3	Cured
2	52	IV	BK virus	1.4	5	Cured
3	20	IV	BK virus	1.0	4	Cured
4	33	III	BK virus	0.9	4	Cured
5	32	III	-	1.2	4	Cured

ADSC = adipose-derived mesenchymal stem cell, HC = hemorrhagic cystitis.

2 died of uncontrolled severe aGVHD, and 2 patients had the same improvement time as patients without MSCs infusion. Therefore, it is difficult to evaluate the therapeutic efficacy. In this study, these 5 cases of HC in our center were all refractory and protracted patients. They were treated with various treatment methods before, and none of disease cases were

relieved. After infusion of ADSCs, satisfactory clinical effects were achieved, suggesting that ADSCs indeed have a good clinical treatment effect on severe HC. At present, in our center, the ADSCs treatment has been mainly used for refractory patients whose disease course lasts for more than 1 month. In the future, it is necessary to carry out long-term close follow-up for patients receiving ADSCs infusion.

For HC patients, combined with previous treatment experience, the stratified treatment ideas of our center are summarized as follows: although Cidofovir is the first-line treatment for BK virus, there is also study showing that when Cidofovir alone for the treatment of BK virus did not show relief of severe HC symptoms.[30] Mert et al[31] reported 3 cases of BK-related HC after allo-HSCT, and they concluded that the treatment with Cidofovir combined with immunosuppressive drugs would be more effective. Therefore, for BK virus and other virus-related HC, on the basis of conventional treatment, the treatment should include reducing or stopping the glucocorticoids and other immunosuppressants, and continuously instilling human immunoglobulin for 3 to 4 days to enhance nonspecific immunotherapy. Bladder epithelium cells are not the classic target organs for the immune damages in aGVHD. Seber et al[5] have retrospectively analyzed 1908 patients after HSCT, and concluded that GVHD was an independent risk factor for LOHC. Lee et al[6] have performed univariate and multivariate analyses, and shown that aGVHD of grades Ⅲ-Ⅳ was a risk factor for LOHC. This may be related to the bladder epithelium being attacked as the target organ of GVHD, as well as the immunosuppressive state related to GVHD increasing the viral reactivation. Therefore, some patients have GVHD before the occurrence of HC, especially when the virus test shows positive finings at diagnosis, which is converted after treatment. If the HC is still severe, the HC may be related to GVHD, and it is recommended to use methylprednisolone intravenous treatment for patients with severe HC. The treatment course is generally 3 to 5 days, which should be ceased when failing. (3) For patients with a long course of disease and prolonged unhealing process, after further excluding other factors, our center recommends active infusion of MSCs. With sufficient treatment course, the overall curative effects should be evaluated after 3 infusions.

5. Conclusion

For allo-HSCT, especially haploid transplantation, the incidence of HC is relatively high. BK virus is the main cause of HC, while GVHD is also related to the occurrence of HC. HC is still a common and potentially life-threatening complication after transplantation. In particular, severe HC can increase transplant-related mortality and have a serious impact on the quality of life of patients. Identifying the risk factors for severe HC is a necessary prerequisite for improving patient prevention and early intensive treatment. Avoiding these susceptible factors could reduce the occurrence and risk of severe HC. Of course, further in-depth studies are still needed to explore the etiology, pathogenesis and treatment methods of HC.

Author contributions

Hailong Yuan: Study Design, Data Collection, Statistical Analysis and Manuscript Preparation; Gang Chen: Data Collection and Manuscript Preparation; Jianhua Qu: Data Interpretation; Ruixue Yang: Data Collection; Maria Muhashi: Literature Search; Gulibadanmu Aizezi: Data Collection; Ming Jiang: Study Design, Fund collection and Manuscript Preparation. All authors have reviewed and approved the final manuscript.

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