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Urological Complications and BK Virus–Associated Diseases Under Allogenic Stem Cell Transplantation

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Key Words

BK-virus · Haemorrhagic cystitis · Nephropathy · Stem cell transplantation · Urological complications

Abstract

Every year 50,000 patients receive a stem cell transplantation worldwide, but there is lack of data pertaining to urological complications. ***Methods:*** We performed a retrospective analysis of all adult patients undergoing their first allogenic stem cell transplantation from January 2011 to June 2013 in our institution. Statistical tests performed were Pearson's correlation, chi-square testing and logistic regression using SPSS 22.0. ***Results:*** We identified 39 patients (22 males, 17 females). Twenty four patients (61.5%) had a urological complication. Most frequent urologic complications were bacterial urinary tract infection (n = 13; 33.3%), acute renal failure (n = 6; 15.4%) and BK virus–associated haemorrhagic cystitis (n = 5; 12.8%). BK viruria was detected in 12 patients (30.8%). We observed an association of creatinine increase (about 20 µmol/l at time of onset of BK viruria) with BK viruria (Pearson's correlation 0.64; p = 0.01), and BK viruria is significantly linked to acute renal failure (Pearson's correlation 0.35; p = 0.029). In univariate regression, BK viruria is significantly linked to urological complication (p = 0.025). ***Conclusions:*** We suggest that BK virus infection during stem cell transplantation can lead to BK virus associated nephropathy, which is so far only known from patients after kidney transplantation.

Introduction

Every year 50,000 patients receive stem cell transplantation worldwide, but there is lack of data about urological complications that occur when this therapy is instituted. Most studies were performed in paediatric stem cell transplantation or are retrospective analyses with a small number of cases [1–7]. The complications mentioned were mostly urological infections and haematuria [8]. Another complication that arises under this therapy is the BK virus–associated haemorrhagic cystitis, which can occur in 5–60% of the cases [9, 10]. This disease can be severe and lead to higher morbidity [11]. In univariate analysis, a myeloablative conditioning regimen has been identified as a risk factor for the development of BK virus–associated hemorrhagic cystitis under stem cell transplantation (p = 0.03, 95% CI 1.25–7.04) [2].

Since urological complications can cause severe problems under allogenic stem cell transplantation with increased morbidity and mortality, further investigations

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especially by urologists are necessary. What is the prevalence of urological complications under stem cell transplantation? When is a urological intervention required? What are the risk factors for the development of urological complications, especially BK virus–associated hemorrhagic cystitis? These questions need to be answered to ensure the quality of urological patient care in stem cell transplantation.

To fill this gap of knowledge, concerning the prevalence and risk factors for urological complications and to generate new hypotheses or research questions, we performed a retrospective analysis of all adult patients undergoing their first allogenic stem cell transplantation from January 2011 to June 2013 in our institution.

Patients and Methods

Development of the Study and Study Population

The study was designed according to the guidelines in the synthesis of qualitative research (ENTREQ) found on the equator-network.org, an international initiative providing robust reporting guidelines [12].

Then all patient records with demographic characteristics, patient history, blood and urine tests, and other related tests of adult patients with haematological disease undergoing their first allogenic stem cell transplantation from January 2011 to June 2013 in our institution were collected. The observation period was from the beginning of conditioning therapy to the end of in-patient stay. In case the in-patient stay was longer than day 70, day 70 after stem cell transplantation was the end of the observation period. No outpatient data were included in this analysis.

Afterward, a data bank of these patients was established.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, a formal consent was not required.

Assessment of Infectious Complications

BK virus was assessed by quantitative PCR in urine (LightMix Polyoma JC-BK, manufacturer Tib Molbiol, Germany) on clinical suspicion only (mainly hemorrhagic cystitis); no other material (i.e. blood samples) was analysed for BK virus. CMV reactivation and urinary tract infections (UTIs) were assessed on a regular basis during in-house treatment. CMV was assessed at least 2 times a week by quantitative PCR; UTI was assessed at least 1 time a week by midstream urine sample and culture, both regardless of clinical signs or symptoms. BK virus–associated cystitis was defined as hemorrhagic cystitis with macrohaematuria in the presence of BK virus in urine.

Statistical Analysis

Statistical calculations were performed using statistical package for the Social Sciences 22.0 software (SPSS Inc., Chicago, Ill., USA). Statistical tests used were Pearson's correlation, chi-square testing and logistic regression.

Day 0 of the timeline was defined as the day of infusion of the stem cell product. Time of leukopenia was defined as the interval from day 0 to the last day after allogeneic transplantation with a leukocyte count $<1.0 \times 10^9$/l. In the same way, time of thrombocytopenia was defined as the interval from day 0 to the last day after allogeneic transplantation with a platelet count $<20 \times 10^9$/l, followed by a transfusion independent increase $>20 \times 10^9$/l.

Results

Demographic Characteristics of the Study Population

We identified 39 patients (22 males and 17 females) undergoing their first allogenic stem cell transplantation due to haematological disease between January 2011 and June 2013 in our institution. The most frequent reason for stem cell transplantation was acute myeloid leukaemia (n = 10; 25.6%) followed by the heterogenic group of non-Hodgkin's lymphomas (n = 8; 20.5%). Urological diseases in patient history were rare. Table 1 shows the basic demographic characteristics of the study population.

Conditioning Regime and Transplantation Data

The conditioning regimens used for allogenic stem transplantation in this study population are heterogenic. Thirty (76.9%) received a myeloablative conditioning and 9 (23.1%) patients were conditioned with a reduced-intense protocol. The mostly used regime for myeloablative conditioning is busulfan/cyclophosphamide/alemtuzumab in 18 cases (46.2%). TBI was used in only 5 cases (12.8%). Seventy four percent of the conditioning regimes (n = 29) contained cyclophosphamide. In-vivo T-cell depletion as GvHD prophylaxis was performed with low-dose alemtuzumab [13] in all patients during conditioning regimen.

Antimicrobial prophylaxis followed standard guidelines. Briefly, the patients received third-generation quinolones, acyclovir, TMP-SMZ and voriconazole or posaconazole [14].

Mesna and forced diuresis were used as prophylaxis in all patients with cyclophosphamide as part of the conditioning regimen.

The transplantation data are shown in table 2. Cyclosporine A (CsA) in conjunction with short-course methotrexate or with mycophenolate-mofetil was used for immunosuppression and GvHD prophylaxis after stem cell transplantation in all patients. Acute GvHD until day 70 occurred in 5 cases: 3 cases were acute GvHD of the skin NCI grade 1, one case acute GvHD of the skin NCI grade 2 and one case acute GvHD of the bowel NCI grade 3. We observed only until day 70 due to the quality of retrospective data.

Table 1. Demographic characteristics of the study population (n = 39)

	n (%)
Gender	
Male	22 (56.4)
Female	17 (43.6)
Age, median	52
SD; min–max	12.97; 20–68
Primary disease	
AML	10 (25.6)
NHL	8 (20.5)
AML arising from MDS	4 (10.2)
CML	3 (7.7)
Plasmoblastic lymphoma	2 (5.1)
MDS	2 (5.1)
Biphaenotypic leukemia	2 (5.1)
Aplastic anemia	1 (2.6)
T-PLL	1 (2.6)
Mantle cell lymphoma	1 (2.6)
Urolocigal disease in patient history	
No disease	26 (66.7)
BOO	3 (7.7)
Urolithiasis	3 (7.7)
CKD	2 (5.1)
Recurrent UTI	2 (5.1)
Pretherapeutic chemotherapy	
Yes	36 (93.3)
No	3 (7.7)
Pretherapeutic radiation	
Yes	6 (15.4)
No	33 (84.6)

AML = Acute myeloid leukemia; NHL = non-hodgkin lymphoma; MDS = myelodysplastic syndrome; CML = chronic myeloid leukemia; T-PLL = T-prolymphocytic leukemia; BOO = bladder outlet obstruction; CKD = chronic kidney disease.

Table 2. Transplantation data of the study population (n = 39)

	n (%)
Donor	
Matched related donor	8 (20.5)
Mismatched unrelated donor	20 (51.3)
Matched unrelated donor	11 (28.2)
Duration of leucopenia, median	14
SD; min–max	4.15; 10–29
Duration of thrombopenia, median	20
SD; min–max	5.49; 8–33
Transfused packed red blood cells, median	6.0
SD; min–max	4.43; 0–20
Transfused packed platelets, median	3.0
SD; min–max	4.96; 0–23
Transfused fresh frozen plasma, median	0.0
SD; min–max	0.65; 0–4
Bearman toxicity kidney	
0	27 (69.2)
1	9 (23.1)
2	3 (7.7)
3	0 (0)
4	0 (0)
Bearman toxicity bladder	
0	36 (92.3)
1	0 (0)
2	2 (5.1)
3	1 (2.6)
4	0 (0)
Acute GvHD	
Yes	5 (12.8)
No	34 (87.2)
Immunosuppression	
CsA + MTX	27 (69.7)
CsA	6 (15.4)
CsA + MMF	4 (10.2)
CsA + MTX + MMF	2 (5.1)

GvHD = Graft vs. host disease; MTX = methotrexate; MMF = mycophenolate mofetile.

We noticed 5 CMV reactivations during the observation period; statistical analysis shows no correlation between CMV reactivation and BK associated hemorrhagic cystitis (Pearson's correlation –0.243, p = 0.136).

Urological Complications

Most frequent complications were bacterial UTI with at least 10^5 uropathogens/ml in midstream urine (n = 13; 33.3%), acute renal failure according to the definition of the Acute Kidney Injury Network (n = 6; 15.4%) and BK virus–associated hemorrhagic cystitis (n = 5; 12.8%). No ureter stenosis was detected in our study population.

In 11 patients with UTI, we found *Escherichia coli* as pathogen, in 2 patients Enterococcus species. In the 2 patients who developed an urosepsis, we found *E. coli* in 1 patient and Enterococcus in 1 patient.

No patient with an acute renal failure needed dialysis or other renal replacement therapies. We found no correlation between acute renal failure and UTIs in our study population (Pearson's correlation 0.298; p = 0.065).

An overview of all urological complications is given in table 3.

Kidney Function and BK Viruria

BK viruria was detected in 12 patients (30.8%). Six patients (15.4%) developed an acute renal failure, 4 of these 6 patients had a BK viruria, and 2 patients developed an acute renal failure in the absence of BK viruria.

There was a median increase of creatinine of 8.0 µmol/l at day 70 after allogenic stem cell transplantation in the group of patients with BK viruria. We observed an association of creatinine increase (about 20 µmol/l at the time of onset of BK viruria) with BK viruria (Pearson's correlation 0.64; p = 0.01) and also a significant association of BK viruria and acute renal failure (Pearson's correlation 0.35; p = 0.029).

BK viruria occurs in mean 28 days after stem cell transplantation (SD 14.05; 20–70).

Figure 1 shows the development of creatinine during stem cell transplantation in comparison of the groups of patients with and without BK viruria.

There is no link between bacterial UTI and BK viruria in this study population (Pearson's correlation –0.17; p = 0.298).

BK viruria is significantly linked to myeloablative conditioning regimen (Pearson's correlation 0.365; p = 0.022) and to donor HLA mismatch (Pearson's correlation 0.354; p = 0.027).

Risk Factors for Urological Complication

In univariate regression, BK viruria is significantly linked to urological complication (p = 0.025). We could not identify a significant risk factor for urological complication in multivariate analysis.

Survival Data

The overall survival is shown in figure 2. There was no mortality due to a urological complication.

Discussion

We performed an explorative retrospective analysis of urological complications under first allogenic stem cell transplantation of adults with haematological disease. To our knowledge this was the first study that focussed only on urological complications under this therapy.

We must assume that this is still a small and heterogenic group of patients undergoing allogenic stem cell transplantation, but urological disease in patient history is rare.

The main urological complications were UTI, acute renal failure and BK virus–associated haemorrhagic cystitis. We found similar results as in retrospective analyses with smaller sample sizes and from paediatric stem cell transplantation [1–7]. Infectious complications like UTI are an expected problem under immunosuppression, and therefore, this result is not surprising.

Table 3. Urological complications of the study population (n = 39)

	n (%)
Urological complication	
Yes	24 (61.5)
No	15 (38.5)
Intervention by a urologist	2 (5.1)
BK viruria	12 (30.8)
Complication	
UTI (significant bacteriuria in midstream urine)	13 (33.3)
Sepsis due to UTI	2 (5.1)
BK virus–associated hemorrhagic cystitis	5 (12.8)
Acute renal failure	6 (15.4)
Pre-renal	1 (2.6)
Renal	5 (12.8)
Post-renal	0 (0)
Presence of BK viruria	4 (11.2)

BK virus–associated haemorrhagic cystitis is defined as BK viruria with the presence of haematuria at the same time; acute renal failure is defined according to the definition of the Acute Kidney Injury Network.

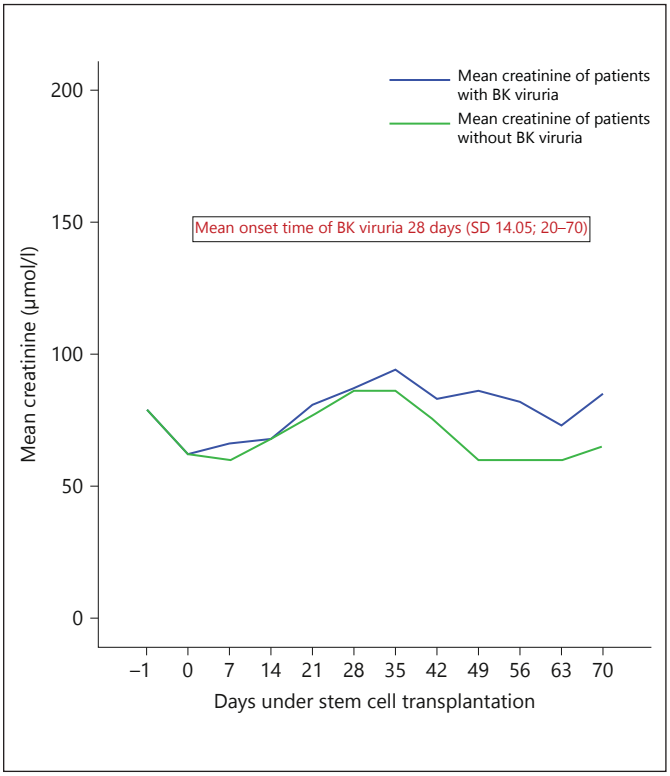

Fig. 1. Mean creatinine development under allogenic stem cell transplantation, comparison between patients with and without BK viruria. –1 day = before starting conditioning regime; 0 day = day of stem cell transplantation.

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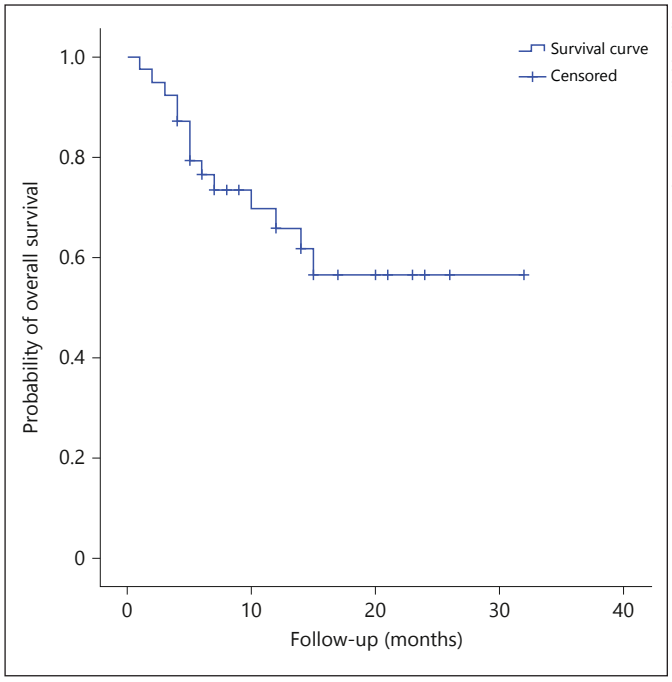

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Fig. 2. Overall survival.

Interestingly, we could identify BK viruria as a risk factor for urological complication in univariate analysis, but we could not find a risk factor in multivariate regression (probably due to the limitations of a multivariate analysis in small sample sizes).

Since we identified BK viruria as significantly linked to urological complication under allogenic stem cell transplantation and BK virus–associated haemorrhagic cystitis was one of the most frequent complications in our study population, we must mention that BK virus–associated hemorrhagic cystitis is a severe problem under stem cell transplantation. It can lead to higher mortality. Gilis et al. [11] showed in their retrospective study of 323 stem cell–transplanted patients that BK virus–associated haemorrhagic cystitis can lead to a significant longer hospitalisation time ($p < 0.0001$), significantly more transfused packed red blood cells ($p = 0.0003$) and significantly more transfused packed blood platelets ($p < 0.0001$). In our opinion, this disease needs further investigation from the urological side. For example, what is the right therapy for these patients?

Several risk factors for BK virus–associated haemorrhagic cystitis have been identified so far: in retrospective studies, myeloablative conditioning, CMV viremia, acute GvHD grades 2–4 and in prospective studies, myeloablative conditioning and acute GvHD again [15, 16]. However, the questions for proper risk stratification and when urological interventions are needed remain to be answered.

The most interesting result of our own analysis is that at the time of BK viruria, there seems to be an impairment of kidney function. From data of kidney transplanted patients, we know that there is also BK-associated nephropathy, which can lead to acute renal failure and even graft loss [16]. In patients after allogenic stem cell transplantation, a correlation between BK viruria and creatinine increase or acute renal failure has not been demonstrated so far.

To our current knowledge, BK virus is a polyomavirus that can lead to BK virus–associated haemorrhagic cystitis especially in patients undergoing allogenic stem cell transplantation and to BK-virus associated nephropathy especially in kidney transplants. It is highly associated with the extent of immunosuppression [10]. We believe that our data give a hint that BK virus infection during allogenic stem cell transplantation in adult patients can also lead to BK-associated nephropathy. Until today there is lack of data in this field.

Of course (as in every retrospective study with a small sample size), we have to assume that our data are biased. On the one hand, 74% of the conditioning regimes used cyclophosphamide, which is highly nephrotoxic and can also lead to haemorrhagic cystitis, mostly earlier than the BK virus, till 14 days after transplantation [10]. In mean the BK viruria occurred 28 days after transplantation in our population and in patients who had BK virus–associated cystitis even later (mean 35 days); so we assume that it is not linked to cyclophosphamide.

On the other hand, we need more data about the immunosuppression and the use of nephrotoxic substances. CsA is always used for immunosuppression in our study population. That is why we suggest that the observed differences in creatinine level are not due to its use in patients with BK viruria.

The creatinine development in our study population (fig. 1) may be interpreted in the following way: the study population starts with a mean normal creatinine in both groups. With the start of the conditioning regimen, creatinine levels fall to a lower normal level in both groups (patients with and without BK viruria) according to the higher fluid intake associated with application of the chemotherapy and the infusion of the stem cell product. After transplantation, mean creatinine rises again mainly due to nephrotoxic substances esp. in immunosuppression, but in the group of patients with BK viruria, its levels stays high and we suggest that BK virus–associated

nephropathy is the reason. In the group of patients without BK viruria, mean creatinine falls again even to a lower level. That might be due to the reduction of immunosuppression and due to a positive selection of patients who survived allogenic stem cell transplantation. Certainly, there are better ways to evaluate kidney function than enzymatic creatinine like in this study population, for example GFR, estimated GFR and Cystatin C; so we need further investigation on a prospective basis to evaluate this issue in the right way.

Because BK virus was assessed based only on clinical suspicion (which means presence of hemorrhagic cystitis in most cases), we may have missed out on subclinical reactivations of BK virus without clinical symptoms. This problem will be addressed in an ongoing prospective trial.

In our retrospective analysis, BK viruria is not linked to bacterial UTI in this group of patients; therefore, we think that BK virus infections are not co-infections with bacterial UTI.

BK viruria is significantly linked to myeloablative conditioning regimen and to donor mismatch. This might be explained by a higher degree of immunosuppression in patients with donor mismatch or myeloablative conditioning. Previous studies also described myeloablative conditioning as a risk factor for BK-associated haemorrhagic cystitis [2].

There was no mortality due to a urological problem. The overall survival data do not differ from what you would expect in a heterogenic group of adult allogenic stem cell transplantation patients [1, 17].

Despite the aforementioned limitations, we believe that our study is important. It is the first analysis of allogenic stem cell transplantation in adult patients only focused on urological complications and it is the first study that demonstrates a correlation between BK-viruria and acute renal failure in this population. Further investigations are necessary, for example to identify more risk factors for urological complications; so a proper risk stratification and even prevention of complications are possible. Still BK virus infections under allogenic stem cell transplantation need more investigation since they can be a severe problem and no causal therapy has been established yet.

Author Contributions

L.S., T.N., M.B. and W.K. participated in the design of the study and critical revision of the article. L.S. and T.N. participated in data acquisition, data analysis and drafting of the article.

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