Brief Communication

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Is BK Virus-Associated Cystitis a Generalized Epithelial Disease?

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Allogeneic stem cell transplantation · Haemorrhagic cystitis · BK virus

Abstract
BK polyomavirus-associated haemorrhagic cystitis (BKHC) is a complication after allogeneic stem cell transplantation, which can occur in 5–60% of the cases. BK viruria alone can also occur in up to 100%. BKHC can lead to severe morbidity in stem cell-transplanted patients, but data about this disease is limited. Consequently, we conducted a prospective unicentric non-interventional trial on BKHC as well as BK viruria after first adult allogeneic stem cell transplantation with a follow-up time of 1 year after inpatient treatment. Between November 2013 and December 2015, we were able to include 40 adult patients with a mean age of 52.8 years. Twenty-seven (67.5%) of these patients were male and 13 (32.5%) were female. Acute myeloid leukaemia was the most frequent underlying disease (n = 15; 37.5%). Only 1 patient developed BKHC during inpatient treatment (n = 1; 2.5%), but BK viruria was frequent (n = 11; 27.5%) during inpatient treatment as well as in the follow-up time (n = 14; 35%). Interestingly, BK viruria was significantly associated with mucositis (p = 0.038) and number of transfused platelet concentrates (p = 0.001). This unexpected association will be discussed and needs further investigation.

Introduction

Every year, 50,000 patients receive a stem cell transplantation worldwide, but there is a lack of data about urological complications that can occur after transplantation. So far, most studies had been performed in paediatric stem cell transplantations or are retrospective analyses with a small number of cases. The complications mentioned were mostly urological infections and haematuria [1]. Another complication that arises under this therapy is the BK polyomavirus-associated haemorrhagic cystitis (BKHC), which can occur in 5–60% of the cases [2]. BK viruria alone can also occur in up to 100%. Hence, research on this issue is of high clinical significance as BKHC can lead to severe morbidity or even mortality in stem cell-transplanted patients [3, 4].

In another retrospective study with 2,477 patients after allogeneic stem cell transplantation, symptomatic BK viruria was also significantly associated with an impairment of kidney function and worse overall survival [5]. Nearly the same had been described before by Gilis et al. [6]. Despite the fact that BK viruria and its complications can be severe and lead to patient morbidity, no causal therapy has been established yet.

Consequently, we conducted a prospective unicentric non-interventional trial on urological complications with a focus on BKHC as well as BK viruria after first adult al-

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logeneic stem cell transplantation with a follow-up time of 1 year (after the end of inpatient treatment). One of the endpoints was to identify associations of BK viruria with main clinical and outcome parameters like overall survival; thus, we report the most interesting results of this evaluation for clinical practice.

Materials and Methods

This is a prospective unicentric non-interventional trial. Before starting the study, we obtained the approval of the local ethics review board at the University Medicine in Greifswald (BB 116/13 from October 8, 2013). The inclusion criteria were patients aged over 18 years receiving their first allogeneic stem cell transplantation due to haematological disease. The use of low-dose alemtuzumab (10 mg at day –2; 20 mg in case of a mismatch) for graft versus host disease prophylaxis was mandatory. No exclusion criteria were defined. From November 2013 until December 2015, we were able to include 40 patients in our study. Statistical calculations were made using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). BK virus load was measured using quantitative PCR (LightMix Polyoma JC-BK, manufacturer Tib Molbiol, Germany). All reported p values were based on a two-sided hypothesis; $p < 0.05$ was considered to be significant.

Results

Between November 2013 and December 2015, we were able to include 40 adult patients with a mean age of 52.8 years. Twenty-seven (67.5%) of these patients were male and 13 (32.5%) were female. Acute myeloid leukaemia was the most frequent underlying disease ($n = 15$; 37.5%). The majority of the patients received intermediate intense conditioning protocols ($n = 31$; 77.5%). BKHC occurred quite seldom: only 1 patient developed this disease during inpatient treatment ($n = 1$; 2.5%), but BK viruria was frequent ($n = 11$; 27.5%) during inpatient treatment as well as in the follow-up time ($n = 14$; 35%).

Interestingly, BK viruria was significantly associated with mucositis ($p = 0.038$; Fisher exact test), the number of transfused platelet concentrates ($p = 0.001$; t test), and the duration of inpatient treatment ($p = 0.048$; t test).

Contrary to our expectations, BK viruria as well as mucositis were not significantly associated with myeloablative conditioning (Fisher exact test).

The median overall survival time was 20.0 months (IQR 12.25–28.75 months). Figure 1 shows the Kaplan-Meier plot of overall survival. In log rank testing, there was no significant difference of overall survival in both groups with or without BK viruria ($p = 0.977$; log rank).

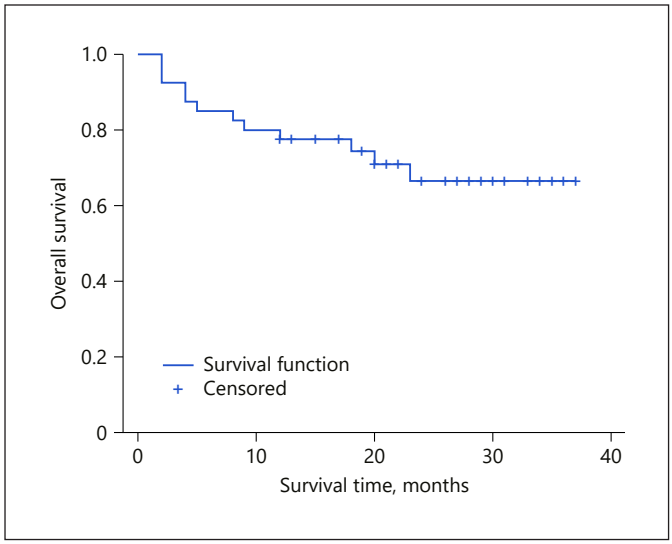

Fig. 1. Kaplan-Meier plot of overall survival of the study population ($n = 40$).

Discussion

We conducted a prospective unicentric non-interventional trial about urological complications after first adult allogeneic stem cell transplantation with a focus on BK virus. To our knowledge, this is one of the first studies specifically addressing this topic.

In our opinion, the most interesting result of this evaluation is the significant association of BK viruria with mucositis. The association of asymptomatic BK viruria with mucositis has been described before in a retrospective study of Peterson et al. [7]. Although this association has been demonstrated before, an explanation is not obvious.

There are two possible explanations for this unexpected but confirmed association: first, a direct causal relationship or, second, the presence of a common confounder. Both, mucositis and BK viruria may be influenced by the degree of epithelial damage induced by the conditioning therapy. In this case, you would expect to see an association between BK viruria and/or mucositis and myeloablative conditioning (which is believed to induce the greatest epithelial damage), but at least in our study this association could not be demonstrated.

Another possible link may be the intensity of immunosuppression induced by immunosuppressive drugs (e.g., cyclosporine A), T-cell depleting antibodies (e.g., ATG or alemtuzumab) or the conditioning regimen itself. With a more intense immunosuppression, you may find

BK replication more often, but reactivation of other viruses contributing to mucositis (e.g., herpes simplex virus) may also be promoted. As the extent of immunosuppression is difficult to quantify, this association may be difficult to prove without a definition of a valid surrogate parameter.

Looking for a direct causal relationship between BK viruria and mucositis, you may speculate about the possibility that BK virus may reactivate in the epithelium in general and BK virus may also be found in oral mucositis. As nobody has addressed this question so far, further investigations will be of interest.

In addition, our study demonstrates a strong association between BK viruria and the number of transfused platelet concentrates. On the one hand, this association can be explained by the patient with BKHC who received 17 platelet concentrates during therapy of his BKHC. On the other hand, BK viruria (without BKHC) is often accompanied by a mild microhaematuria only detectable by urinalysis, representing a subclinical BK cystitis not leading to macrohaematuria, but strong enough to induce a consumption of platelets by a localized activation of the coagulation system at the bladder surface. Consequently, we have to further analyse these cases of microhaematuria with a focus on virus replication and blood counts. Additionally, platelet consumption can also occur in mucositis even when it is happening at the same time as BK viruria.

On the whole, we suggest with these data that BK reactivation might occur as a generalized problem in the epithelium; however, further investigations of the association of BK virus and mucositis are necessary, e.g., the analysis of pharyngeal washes with quantitative PCR on BK virus replication.

Furthermore, even if this is one of the first prospective studies, we assume that our data have some limitations such as the unicentric study population. The association of BK viruria with mucositis and maybe an occult blood loss is new and very interesting.

Acknowledgment

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Statement of Ethics

This study was approved by the ethics review board at the University Medicine in Greifswald (BB 116/13 from October 8, 2013). Informed consent was given to every patient.

Disclosure Statement

All authors declare that they have no conflict of interest regarding the manuscript.

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Author Contributions

All authors were involved in the design of the research, collecting and analysing the data. L.S., T.N., and W.K. wrote the manuscript.

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