*Review*

# Full Myeloablative Conditioning and an Unrelated HLA Mismatched Donor Increase the Risk for BK Virus-positive Hemorrhagic Cystitis in Allogeneic Hematopoetic Stem Cell Transplanted Patients

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**Abstract.** *BK virus (BKV)-associated hemorrhagic cystitis (HC), varying from mild hematuria with or without dysuria to life-threating bleeding and clots that may cause urinary obstruction and renal failure, causes significant morbidity and mortality in haematopoetic stem cell transplanted (HSCT) patients. Unfortunately, its development is difficult to predict since BK viruria is very common after HSCT and can be present in patients with and without HC. There is therefore the need to identify risk factors that may increase the risk of developing HC after HSCT. The viral load of BK-viruria, as well as BK viremia, has been monitored for this purpose. Moreover, having full myeoblative conditioning (MC) versus reduced intensity conditioning (RIC) prior to HSCT and an HLA-matched or -mismatched graft from an unrelated donor in contrast to an HLA-matched graft from a related donor have been studied as risk factors for HC. In addition, graft versus host disease has been examined, but has not been defined as a definite risk factor for HC. We conclude that the present evidence suggests that HSCT patients with BK viruria, receiving MC and an unrelated donor graft that is HLA-mismatched have an increased risk for developing HC in comparison to patients receiving RIC and an HLA-matched related donor graft.*

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*Key Words:* Hemorrhagic cystitis, allogeneic stem cell transplantation, BK virus, review.

BK virus (BKV)-associated late-onset hemorrhagic cystitis (HC) after allogeneic hematopoetic stem cell transplantation (HSCT) in patients with leukemia or other diseases is still a serious cause of morbidity and can also result in mortality (1-4). During the transplantation period, HSCT patients go through severe immune suppression in order to accept the graft, avoid graft rejection, and acute graft-*versus*-host disease (aGVHD) (5). Hence, HSCT patients are extremely susceptible to infection in general, as well as reactivation of latent viruses (6). BKV is one of these latent viruses, and reactivation of BKV and BK viruria is, for example, associated with late onset HC (7-10). However, since BK viruria is common in patients both with and without HC, there is a need to identify co-factors that may predict increased the risk for HC, be it the extent of BK viruria or viremia, the conditioning regimen, the donor source, or aGVHD. Here, we summarise the present view on the disease and co-factors that today are regarded as relevant or irrelevant for an increased risk for the development of late-onset BKV associated HC. In addition, we deal with some aspects of management.

## BK Virus

BKV belongs to the polyomavirus family (11) and was first described in the urine of a renal transplant patient (12). It is a small double-stranded DNA virus with a genome of around 5 kbp arbitrarily divided into a non-coding control region (NCCR) and an early and a late region. The NCCR comprises the origin of replication and the promotor/enhancer regions and includes different binding motifs for cellular transcription factors (11, 13). The early region

encodes the large T and small t antigens. Large T is necessary for stimulation of cellular DNA synthesis and the establishment and maintenance of cellular transformation, while the function of small t is less well understood, but it seems to be important together with large T for replication (11). The late region codes for the viral capsid proteins VP1, VP2 and VP3 and the agnoprotein (11).

## Clinical Features of BKV Infection

The exact route for transmission of BKV is unknown and there is no evidence that primary BKV infection is associated with clinical illness, however seroepidemiological studies show that infection occurs in childhood and that specific antibodies are present in 90% of all adults (11). Moreover, after primary infection polyomavirus remains latent (*e.g.* in the kidneys, peripheral blood and brain) and can be reactivated both in healthy individuals and during immunosuppression, which can be manifested by symptom-free shedding in the urine (14-17). In immune-compromised transplant patients, BKV reactivation can become more severe and manifest itself as HC in allogeneic HSCT patients, or as polyomavirus-associated nephropathy (PyVAN) in renal transplant patients (18). In both these diseases, it is obvious that the fact that the patient has an allogeneic transplant plays a role, but most likely additional factors are involved (3, 4, 18, 19).

## Diagnosis of BKV Infection

Diagnosis of pre-transplant BKV exposure is performed by serology and anti-BKV antibodies can be detected by hemagglutination inhibition, or IgG- or IgM-based ELISA (11, 20, 21). This is however rarely useful in transplant patients since the majority of infections occur in early childhood. Detection of BKV DNA by nested PCR or quantitative PCR is sensitive and useful to identify BKV reactivation manifested as *e.g.* BK viruria or viremia (7, 12, 22-25).

BKV-associated HC usually occurs between 1 week to 6 months after HSCT, and is classified as late-onset HC, to distinguish it from early-onset HC, occurring 48 to 72 hours after HSCT which is caused by the conditioning regimen *e.g.* total body irradiation, or treatment with busulfan or cyclophosphamide (4, 19, 26). Late onset HC is mainly associated with BKV reactivation, but also adenoviruses and other viruses have been described to cause HC (19, 27). Primary BKV infection due to transmission of BKV during HSCT has also been suggesed as a cause of HC, but this possibility was dismissed, since most patients and donors were BKV positive by serology and the findings indicated that BKV infection was more common than aniticipated (21). An association between BKV mutants and HC was studied in a pilot study, and BKV mutants with C→G mutations in the Sp1 binding site within the NCCR were significantly over-represented in the urine of HC patients, as compared to their absence from patients without HC (28). However, these studies were not pursued.

HC can be graded according to several similar systems (4) as suggested *e.g.* according to Bedi *et al.* (8); grade 1, microscopic hematuria; 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. Additional criteria are dysuria and lower abdominal pain.

Most HC cases resolve. However, in severe cases, the bleeding may be life threatening and concurrent complications can contribute and result in fatal outcome. Hence, BKV-associated HC causes significant suffering, as well as mortality, and prolongs hospital care considerably. To identify patients at risk may be the first step in intervening with the course of the disease.

## BK-viruria is Associated with an Increased Risk for HC in HSCT Patients, but it Is Not Diagnostic for HC, and a High BKV Load in the Urine is Indicative but not Diagnostic for HC

Around half to all HSCT patients present BK viruria at some time after HSCT, and about 4-25% of the patients develop HC (4, 7-10, 19, 24, 27, 29). BK viruria is usually observed around 2-8 weeks' post-HSCT and may last 1 week to 2 months, which also parallels the development of late onset HC (4, 19). The association of BK viruria and HC in time, in the absence of other infections, and the observation of polyomavirus inclusions in uroepithelial cells of HC patients suggests that BKV is involved in HC (1-4, 19). There is by now substantial accumulated evidence for a correlation between BK viruria and HC (4, 7-10, 19, 24, 27, 29, 30).

To obtain a more accurate diagnosis or prediction for the development of HC, BK viral load has been assessed (23, 25, 31-33). Quantification has been performed by BKV DNA-specific real-time quantitative PCR (23, 25, 31-33) and several other reports have suggested that a high viral load may be indicative of HC, especially when there is a very high viral load, such as $>10^6$ BKV copies/μl urine (10, 23, 25, 31). Nevertheless, it has not been possible to use a high viral load determined by Q-PCR as a diagnostic test for HC (10, 23, 25, 31).

The occurrence as well as the quantity of BKV DNA in peripheral blood lymphocytes, plasma, and serum in correlation to HC has also been assessed (32, 33). However, although BKV DNA has been found in blood samples of allogeneic HSCT patients, neither its presence or quantity appears to be diagnostic for the development of HC.

## Patients Receiving Full Myeloablative Conditioning (MC) Prior to HSCT Have a Greater risk for HC Compared to patients Receiving Reduced Intensity Conditioning Regimen (RIC) and having an Unrelated Donor (URD) and MC Presents a Special Risk

Recent studies have examined the role of myeloablative conditioning (MC) prior to HSCT *versus* reduced intensity conditioning (RIC) regimen, as well as donor type and the development of HC (34-37). In two recent studies, where one was a follow-up of the other, both BK viruria and HC were significantly more common in patients receiving MC as compared to patients receiving RIC (36, 37). In the first of these studies, 90 HSCT patients were included (36). In the second study, 175 HSCT patients (179 HSCT events) were followed for the influence of the conditioning regimen, donor background and HLA matching on the development of BKV-associated HC and this study provided us with additional data (37). In the larger latter study, 27 patients presented late-onset HC and BK viruria was verified in 23/27 HC events. Seventy-one (40%) HSCTs were performed with MC, while 108 (60%) were performed with RIC, and 66 (37%) patients received a related donor (RD) graft and 113 (63%) an unrelated donor (URD) graft.

Independent risk factors for HC by multivariate logistical regression analyses were BK viruria (OR 6.7; 95% CI 2.0-21.7; $p$=0.001), or MC (OR 6.0: 95% CI 2.1-17.3; $p$<0.001) and URD (OR 3.4; 95% CI 1.1-10.6; $p$=0.03). BK viruria was more frequent during HC than non-HC events, and after MC as compared to RIC (both $p$<0.001), and with an HLA-mismatched donor ($p$<0.01).

MC was thus confirmed as an important risk factor for the development of HC and, analoguous to previous studies, having a URD graft was associated with HC, both by univariate and multivariate analysis (34-37). Moreover, having an HLA-mismatched donor was more frequent in HSCT patients acquiring HC (37).

However, when analysing HSCT performed with URD or RD grafts separately, some significant differences were observed. Having BK viruria (OR 8.5; 95% CI 1.8-19.3; $p$=0.004) and MC (OR 5.9; 95% CI 1.3-11.3; $p$=0.009) increased the risk for HC with a URD graft, but not with an RD graft (37). Having an HLA mismatch was also identified as an independent risk factor for HC only in the URD setting and not with an RD graft (37).

The significance of donor type for development of HC in allogeneic HSCT was also studied earlier by El Zimaity *et al*. (35). In this study, 105 acute leukemia patients treated between 1990-2001 with 12 Gy total body irradiation-based regimens (MC) were followed up. However, in this early study, the influence of conditioning regimen could not be assessed since patients all received MC. A total of 38 patients received grafts from URD, 15 patients received cord blood grafts (UCB), 20 received mismatched RD grafts, and 32 received matched RD grafts. A significant increase in HC in patients transplanted from URD and receiving UCB was evident the first month. Moreover, patients with an RD had less HC than those receiving a URD graft. Furthermore, there was no evident difference in the incidence of HC in patients receiving bone marrow or peripheral stem cells, while in this and the other studies, the incidence of HC in patients receiving UCB was the highest *i.e*. 40-50% (34-37).

The pathogenesis of late-onset HC in relation to conditioning and donor graft is thus still enigmatic. It has been shown that there is a higher risk for HC after allogeneic HSCT as compared to autologous HSCT. We have suggested that the immunosuppressed state of the patient is important since HSCT patients with URD grafts have a higher risk for HC than those with RD grafts. Whether this is an effect of the increased immunosuppression regimen often used for patients receiving URD grafts or a direct effect of HLA mismatching, for example, through an immunopathological mechanism is unknown. Another hypothesis is that patients undergoing MC and receiving URD grafts risk HC due to the combination of more intensive conditioning regimens, which then increases the risk for BK viruria. In this situation, adding an HLA-mismatched donor graft, and more immune suppression result in further cell damage and BK viruria, and in turn to a further increased risk for HC. This is consistent with the evidence that after RIC, there is a greater retention of the patients' immunity early after HSCT, allowing for a more gradual switch to donor immunity against BKV. This hypothesis is supported by the fact that BK viruria was less common during HSCT events with RIC and is supported by studies of other viral infections, such as CMV, which also show lower rates and disease early after an RIC HSCT (19, 36, 37, 38).

In summary, BKV-associated late-onset HC and BK viruria are more common in patients receiving MC compared to patients receiving RIC. The reason for this is suggested to be due to RIC being less toxic than full conditioning, and may possibly maintain recipient immunity longer, hence reducing the incidence of BK viruria and HC.

## Acute GVHD Alone Has Not Been Confirmed as a Co-factor for the Development of HC

Early studies have suggested aGVHD as a cofactor for the development of HC (3, 39), but this was not confirmed in several later studies (4, 35, 36). However, the pathogenesis of post-engraftment HC after HSCT has been suggested by Leung *et al*. (10) to partly be due to uroepithelial damage by chemotherapy/irradiation, polyoma BKV infection, as well as alloimmune reactions. In this hypothesis, the alloimmune reactions of donor lymphocytes may be stronger, especially with URD, and possible HLA

mismatches, resulting in possibly donor lymphocytes targeting target the recipient uroepithelial cells and causing epithelial damage. This hypothesis would be that components of aGVHD, although not alone, may still contribute to HC development (10).

## Management

There is still no specific treatment for BKV infection or late-onset BKV-associated HC. Treatment of HC is mainly asymptomatic (4, 40-42). HC may require analgesia, and patients with macroscopic hematuria are recommended hyperhydration and forced diuresis. In more severe HC cases, blood transfusions may be needed and urological intervention is necessary to avoid renal failure due to massive clotting (26). There are smaller studies that suggest positive effects of antiviral agents, but formal randomized trials with different antiviral agents have not been conducted. The use of low-dose cidofovir for BKV-associated HC has been suggested and may be somewhat effective (43, 44), but a randomised controlled trial is needed to assess its usefulness. The use of mesenchymal cells has also been suggested, and in a pilot study the introduction of mesenchymal cells was suggested to abrogate HC, but here the evidence is also limited regarding their efficacy (4).

## Conclusion

The data suggest that BKV reactivation with BK viruria is associated with the development of late-onset BKV-associated HC in allogeneic HSCT patients. However, neither BK viruria or a high viral load are diagnostic for HC, although a very high viral load $>10^6$ BKV copies/μl urine is indicative of risk for HC. MC presents a higher risk for HC as compared to RIC and having MC and URD, and an HLA-mismatched donor further increases the risk for HC. Acute GVHD has not been consistently shown to be an important factor for the development of HC.

Our present hypothesis is that late-onset BKV-associated HC develops through: i) uropithelial damage due to various causes *e.g.* chemotherapy, irradiation, thus inducing inflammation, regeneration and BKV reactivation after *e.g.* MC; ii) BKV reactivation is intensified as a result of increased immunosuppression due to MC; and iii) that non-stringent allo-immune reactions from donor lymphocytes due to *e.g.* HLA mismatches emphasize immune suppression as well as their targeting polyomavirus-infected recipient uroepithelial cells causing further damage and further BKV reactivation. Management is still symptomatic, and although there are some data that suggest that antiviral drugs may be of use, prospective trials are warranted.

## Acknowledgements

This work was supported in part by the Swedish Children's Cancer Foundation, the Swedish Cancer Foundation, the Stockholm Cancer Society, the Felix Mindus Foundation, the Stockholm City Council and the Karolinska Institutet.

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*Received February 4, 2011*
*Revised February 18, 2011*
*Accepted February 21, 2011*