Review Article
Treatment protocols for BK virus associated hemorrhagic cystitis after hematopoietic stem cell transplantation

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Abstract: Hematopoietic stem cell transplantation (HSCT) represents a vital curative choice for many disease. However its outcome can be hampered by a variety of transplant associated complications. Hemorrhagic cystitis (HC) considered as one of the major difficulties after HSCT. HC symptoms comprise hematuria, dysuria, burning during urination, urinary frequency, urgency and incontinency, abdominal or suprapubic pain, urinary obstruction, and renal or bladder damage. There are a lot of causes for HC development. BK virus reactivation is one of the major causes of HC after HSCT. There is still no standard and approved treatment protocol for BK virus associated HC (BKV-HC). Treatment of HC is according to the local standard operating procedures, depending on the cause and severity. In this study we will review the current treatments available for this disease. We have divided the therapeutic procedures into 5 categories including conservative therapy, complimentary options, surgical procedures, pharmacological treatments and adoptive cell therapy. We believe that comparing the advantages and disadvantages of different therapies make it easier to choose the best treatment protocol. In addition, we had a greater focus on adoptive cell therapy, because it is a relatively new introduced method and might be a logical alternative to conventional treatments for refractory patients. In total, no definitive recommendation is possible for current available treatments because these procedures have only been utilized sporadically in a limit number of patients. Furthermore, a number of treatment options are only experimental and definitely need more effort.

Keywords: BK virus, hemorrhagic cystitis, hematopoietic stem cell transplantation, cidofovir

Introduction

Hematopoietic stem cell transplantation (HSCT) represents a vital curative choice for patients with a large group of malignant disorders such as leukemia and lymphoma, and nonmalignant conditions mainly metabolic diseases and immunodeficiency syndromes. Nevertheless, the outcome can be hampered by a variety of transplant associated complications [1-4]. HSCT can cause a transient severe immune deficiency in patients which last about three to six months [5]. Infections that can be caused by various types of microorganisms are a major root of mortality and morbidity during this phase of immune deficiency. Overall, 11% of post HSCT deaths are caused by infections, with one-third of these being viral infections [5]. A number of challenging viruses after HSCT include human adenovirus (Adv), Epstein-Barr virus (EBV), human cytomegalovirus (CMV), and BK virus [3, 5]. The latter is one of the main cause of Hemorrhagic cystitis (HC). Hemorrhagic cystitis (HC) considered as one of the major difficulties after HSCT. HC symptoms differ from microscopic to macroscopic hematuria with or without clots, dysuria, burning during urination, urinary frequency, urgency and incontinence, abdominal or suprapubic pain, urinary obstruction, and renal or bladder damage [6-8]. HC is classified into four grades according to its severity: microscopic hematuria (grade 1), macroscopic hematuria (grade 2), hematuria with clots and need for transfusion product (grade

3), hematuria with clots and impaired renal function (grade 4) [8, 9]. It is also divided according to the time of incidence into two groups: Early-onset HC, occurs during 1 week after HSCT. This complication is the result of toxic effects caused by conditioning regimen with cyclophosphamide, busulfan and etoposide and their metabolites and also total body irradiation [9]. Late-onset HC, arises between 2 to 8 weeks after HSCT, is concomitant predominantly with certain viruses such as BK and JC polyoma virus, adenovirus type I and II, and cytomegalovirus (CMV) [8, 9]. A wide spectrum of prevalence rates for HC have been reported. A recently published systematic review has been described that BK viruria arises in 25 to 100 percent of stem cell transplanted patients [10]. High levels of BK viruria are associated with a higher risk of developing HC. It can lead to BK Virus associated hemorrhagic cystitis in up to 40 percent of patients [10]. Since BK virus reactivation is one of the major causes of HC after HSCT and there is still no standard and approved treatment protocol for BK virus associated HC (BKV-HC), in this study we will review the current treatments used for this disease. We believe that comparing the advantages and disadvantages of different therapies make it easier to choose the best treatment protocol.

BK virus pathogenesis, prevalence, diagnosis and risk factors

BK virus is a member of the polyoma viridae family. It has a small, nonenveloped, icosahedral capsid with major proteins virion protein 1 (VP1), VP2, and VP3. This virus leads a common childhood infection with any particular clinical symptoms. Sometimes it can cause a mild respiratory disease. Following recovery of primary infection, the virus hides in the renal tubular and uroepithelial cells [11, 12]. About 80 percent of adults are seropositive for BKV and occasionally it can be reactivated and manifest as asymptomatic viruria [11, 13-15]. BKV reactivation predominantly occurs in immunocompromised individuals and causes significant mortality and morbidity. The main clinical symptoms after BKV reactivation are BKV associated nephropathy (BKVAN) or ureteric stenosis in Kidney transplant recipients (KTR) and hemorrhagic cystitis (HC) in hematopoietic stem cell transplant recipients [7, 11, 14, 15]. Other rare clinical manifestations related to BKV reactivation include meningoencephalitis and interstitial pneumonitis [16, 17]. Quanti-

tation of BK viral load in the urine, plasma or cerebrospinal fluid (for Central nervous system (CNS) involvement) with PCR is the standard clinical method for evaluating BKV reactivation. In recent years, measurement of BKV mRNA levels in plasma or urine has been introduced as a highly specific and sensitive method for the detection of active BKV replication [11]. Having comprehensive information about the pathogenesis of a disease is important in guiding potential management strategies. The pathogenesis of BK-HC is less well known. It has been proposed to result from a series of co-operating events. First, conditioning regimen (Chemotherapy or irradiation) causes subclinical damage to the bladder mucosa and provide a permissive environment for BKV replication. Then, during the immunosuppression phase, BKV reactivation occurs and its uncontrolled replication in urothelial cells may further causes denudation of the injured bladder mucosa. Finally, the immune attacked by innate immune signals to cytopathic denudation or T lymphoid cells against BK viral antigens perpetuate mucosal damage [9, 13, 18-20]. Therefore, it can be concluded that the cooperation of conditioning regimen, immunosuppression and inflammation together may result in development of BKV-HC after HSCT. A number of risk factors associated with BKV-HC development are listed in **Table 1**. Several studies have attempted to recognize risk factors associated with BKV-HC. There is consensus on several factors, but recipient age and GVHD are still controversial. Although young age is not expected to be a risk factor for BKV-HC development, in several studies it has been identified as a risk factor [21]. Age below 40 and 7 years were significantly associated with increased risk [9, 21]. While in several studies a significant association between occurrence of BKV-HC and aGVHD were observed [21, 22], no correlation was found in a study conducted by L Gilis [23]. In one of the studies, acute GVHD grades II to IV were more common in HC patients than in non-HC patients [24]. Time-dependent aGVHD grades III to IV has been reported to be an independent risk factor for severe BKV disease in Nienke M.G.Rorije's study [25].

Treatment

Treatment of hemorrhagic cystitis is according to the local standard operating procedures, depending on the cause and severity [6, 11].

Table 1. Risk factors associated with BKV-HC development

Risk factor	Increased risk	Decreased risk	Reference
Type of transplantation	Allogeneic especially after haploidentical	Autologous	[9, 54, 93]
Type of donor	Unrelated donor	Matched or mismatched related donor	[9, 13, 54]
Stem cell source	Cord blood or peripheral blood	Bone marrow	[9]
Age of transplant	>7 years	<7 years	[9]
Conditioning regimen	Myeloablative	Reduced intensity	[9, 13, 21, 54]
BK viruria	Urine BKV load >10^7 gEq/ml	-	[9, 13, 93]
BK viraemia	Blood BKV load >10^3 gEq/ml	-	[9]
Acute GVHD	Grade II-IV	-	[9]

Prevention probably is the best treatment of hemorrhagic cystitis [26]. Early onset HC has become rare due to the use of preventive measures such as urine alkalization, hyperhydration and the frequent use of 2-mercaptoethane sodium (MESNA) [27, 28]. MESNA can inactivate acrolein, which is the main toxic metabolite of cyclophosphamide. Therefore, it is considered as an uroprotective agent [27]. Many patients with HC can be treated with these procedures, but refractory patients may require further measures. In addition, HC due to viral infection can be treated with anti-viral agents, but their efficacy is limited. Most cases of BKV-HC are mild and self-limited, but there are no standard and approved treatments for severe episodes of BKV-HC [11, 29]. In this review we have divided the therapeutic procedures into 5 categories including conservative therapy, complimentary options, surgical procedures, pharmacological treatments and adoptive cell therapy. In the following we will discuss the treatments available in each category with a greater focus on adoptive cell therapy, because it is a relatively new introduced method and might be a logical alternative to conventional treatments for refractory patients. Clinical trials for HC are listed in **Table 2**.

Conservative therapy

Conservative therapies, also known as supportive approaches or symptomatic therapies, are considered as preventive and the first steps of therapy in most centers. These include forced hydration, spasmolytics, analgesics and symptomatic pain relief treatment [6, 11]. A prospective, randomized study compared hyperhydration plus forced diuresis versus standard hydration plus mesna as prophylactic option. The incidence of HC was almost similar in both groups (26.8% and 23.7%, respectively) [30].

Conservative therapies are not effective in severe cases.

Complimentary options

In more severe cases (grades 2 and 3 HC), complimentary options described below are used:

- *Optimization of the hematological homeostasis* including the use of clotting factors (recombinant factor VIIa or VIII, factor XIII) and antifibrinolytic agent aminocaproic acid [6, 11]. A number of authors proposed the application of fibrin glue via an endoscopic spray applicator on the bleeding bladder mucosa. Its application apparently diminish the hematuria and the voiding symptoms regardless of the bleeding etiology [31-33]. The cumulative incidence of pain termination and complete remission, was 100% and 83%, respectively, in a published paper after the application of fibrin glue [33]. Another blood product that recently have been used for HC patients is platelet rich plasma (PRP). It is fundamentally an increased concentration of autologous platelets suspended in a small volume of plasma after centrifugation [28, 34]. This product also named autologous platelet gel, plasma rich in growth factors (PRGF), and platelet concentrate (PC). Platelets play a vital role in hemostasis and are an important source of growth factors [28, 34]. It is well known that PRP has a potential beneficial role on the therapeutic angiogenesis and tissue formation. PRP is applicable in several clinical fields including in the management of skin wounds [35]. Lorenzo Masieri and colleagues proposed a novel endoscopic technique for the management of BKV-HC after HSCT [28]. They used the intravesical instillation of PRP compound on the bladder mucosa after an electrocoagulation of the bleeding areas [28].

Table 2. Clinical trials for HC

Purpose of study	Recruitment Status	Enrollment (participants)	Phase	Interventions	ClinicalTrials.gov Identifier	Time of study
To evaluate the absorption, safety and tolerability. Conditions: BKV-HC	Completed	6	1	Cidofovir + Probenecid	NCT01816646 [94]	2013-2016
To learn if adding cidofovir to the standard of care can improve symptoms. Conditions: BKV-HC	Active, Not recruiting	27	2	Standard of Care + Cidofovir versus Standard of Care	NCT01295645	2011-2022
To assess the safety and tolerability of three different doses. Conditions: HC	Not yet recruiting	18	2	LP-10 (Intravesical tacrolimus) versus Placebo (normal saline)	NCT03129126	2020-2021
To evaluate Viralym-M for resolution of HC compared to placebo. Conditions: BKV-HC	Not yet recruiting	125	3	Biological: Viralym-M versus placebo	NCT04390113	2020-2022
To evaluate the safety and efficacy. Conditions: HC	Completed	12	1/2	Biological: Decidual Stromal Cell therapy	NCT02172963	2011-2013

The basis of using PRP is to induction of hemostasis along with accelerating vascularization, improving wound healing and tissue repair. Overall, 60% of the patients presented a complete response to the treatment with no reported intraoperative complications [28]. Therefore, this novel technique seems to be safe, feasible, non-invasive and reproducible option for the treatment of BKV-HC. According to validated questionnaire, in almost all the patients a pain relief along with a disappearance of dysuria, urgency and frequency was observed [28]. All of these methods are used to optimize the homeostasis and reduce bleeding. But if the bleeding continues and leads to anemia, blood transfusion should be considered [11].

- *Continuous bladder irrigation and intravesical therapy* to instill solutions and medications directly into the bladder. These procedures can be applied regardless of the cause of HC. In the absence of obstructing clots, simply hydration with saline solution may be the only treatment required [26, 36]. If the clots obstructing the bladder outlet, clot removal is indicated. Normal saline continuous bladder irrigation is started after clots are evacuated. It can help to avoid further clotting [36]. If the disease persists, the bladder can be irrigated with a variety of agents including chondroitin sulfate, sodium hyaluronate, prostaglandins (PGE1, PGE2, and PGF2α), formalin, and alum [6, 9, 26, 36, 37]. In one of the studies that used intravesical instillation of sodium hyaluronate, five out of the seven patients achieved complete response and any local or systemic adverse effects were observed [38]. It has been reported that alum irrigation can resolve the hematuria in 60-100% of patients, completely. Because it causes vasoconstriction and decreased capillary permeability [39]. However, these agents are mostly used for non-viral causes of HC and their efficacy in viral causes is not yet fully understood. In addition, they are not totally without risk and constant monitoring of patients is required [6, 11, 36].

- *Systemic treatments*: Patients can be treated with intravenous or oral pentosan polyphosphate and sodium pentosan polysulphate [6, 11]. They have been broadly used for managing interstitial cystitis. In patients with interstitial cystitis, epithelial permeability, is increased. These agents can substitute surface glycosaminoglycans which have been lost, and con-

sequently reverse the surface damage [40]. In addition, the bladder epithelium is less vulnerable to bacterial adherence and the causes of hematuria are decreased [40]. However, it is more commonly a choice for managing HC secondary to radiotherapy or chemotherapy than virus induced HC [40]. Intravenous or oral estrogen is another type of available medications. Estrogen can influence the microvascular stability in the bladder wall [41]. Although many published studies demonstrated positive outcomes (70% [42] and 80% [41] significant improvement in hematuria), its effectiveness in the treatment of virus associated HC is controversial [43].

- *Hyperbaric oxygen therapy (HBO)* is a non-invasive technique involving the application of 100% oxygen under increased pressure [27, 44, 45]. It can penetrate to poorly perfused regions. HBO is applied as primary or complementary therapy for many medical situations in which tissue damage is caused by hypoxic injury [27, 44, 45]. The mechanism of HBO therapy in HC after radiation is well known. It leads to efficient saturation of patient's tissue. Thereby induced proliferation of fibroblasts, promoted angiogenesis and wound healing. So the damaged hypoxic urothelium will be recovered [27, 44, 45]. HBO therapy have been used in several studies for the treatment of BKV-HC [46-48]. In one study that the HBO therapy was used as the last treatment step, it was a well-tolerated, sufficient and effective method with good clinical and laboratory results and any severe adverse events [44, 45]. In accordance with previous study, Savva-Bordalo and colleagues observed clinical resolution of hematuria in 94% of their BKV-HC patients after HBO therapy [27]. Also, they reported more rapid responses in patients who started HBO therapy earlier after HC diagnosis. They found that BK viruria was largely lower after HBO therapy, which can be related to better outcomes [27]. However, prospective, randomized and well-controlled trials are required to establish its definitive efficacy and safety.

Surgical procedures

In very severe cases, as last step of treatment, urological intervention and surgical management such as bilateral percutaneous nephrostomy tubes with or without ureteral occlusion, selective arterial embolization, cauteri-

zation, fulguration and total or partial cystectomy should be considered [6, 11, 49]. Kazuhiro Kurosawa especially indicated that transurethral electrocoagulation (TUC) can be considered for BKV-HC, but total cystectomy should be avoided [50].

Pharmacological treatments

Currently, there are no specific antiviral treatments with strong evidence of clinical efficacy against BKV. The typical clinical method upon identification of BK viremia is gradual reduction of immunosuppression regimen, to simplify reestablishment of BK virus specific T cell [11]. Then, the BK viral load in the blood is serially monitored by PCR [11]. Reducing immunosuppression after allogeneic HSCT increase the risk of acute rejection and exacerbating graft versus host disease (GVHD). Furthermore its long term consequence is a higher incidence of chronic rejection [11]. Several agents have been described to affect the virus replication and can be applied as treatment options. These substances generally have been combined with immunosuppression reduction [11, 29, 51].

- *Cidofovir (CDV)* is a nucleotide analog of cytosine. It acts against a broad spectrum of DNA viruses including herpesviruses and polyomaviruses and is licensed by FDA in the United States as an intravenous second line treatment for CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS) [51-53]. During DNA synthesis, the viral DNA polymerase incorporates CDV into the nascent DNA strand, it leads to slow DNA synthesis in subsequent steps [51, 53]. Therefore a reduction in viral replication is expected. CDV has the highest specificity against BKV. It is currently the frontline drug for the treatment of BKV-HC, but its intravenous application is frequently limited by nephrotoxicity especially in higher doses [51, 54, 55]. This drug is not available in the majority of countries and it is a high price drug. Because of nephrotoxicity adding probenecid to CDV as a nephroprotection agent is recommended. The standard intravenous (IV) dose of cidofovir is 5 mg/kg weekly. Overall, CDV is applied in normal dosing (3-5 mg/kg) or low dosing (0.25-1.5 mg/kg), with and without probenecid [51, 54, 56]. The application rates and the administration route of CDV is weekly or other rates and intravesical or intravenous tre-

atments, respectively [51, 56]. Most studies used 5 mg/kg CDV diluted in 60 ml normal saline instilled for 60 minutes into the bladder, for intravesical CDV treatment [51, 55, 57]. Despite bladder spasm and discomfort during instillation have been reported in a number of studies, the main benefit of local administration route is less nephrotoxicity [55, 58].

In a retrospective study, CDV (5 mg/kg/weekly) was administered intravenously and the reduction of BK viruria, improvement of HC grade and a complete clinical response was documented 87%, 70% and 51%, respectively [59]. A review article published in 2015 reported the results of 13 studies that used CDV for BKV-HC. Overall, between 60 and 100 percent of complete remission were observed regardless of CDV dose or administration route [60]. The clinical trials that used CDV, are listed in **Table 2**. It should be noted that in a number of published papers, while the significant clinical improvement were observed in BKV-HC patients, there were no significant changes in BK viremia or viruria [55].

- *Brincidofovir (BCV or CMX001)* is an ether lipid ester conjugated prodrug of CDV. It is an orally administered drug with lower incidence of nephrotoxicity that presently undergoing phase III clinical trials [11, 51, 61-63]. The attractive pharmacokinetic properties of BCV including rapid uptake by cells and possibility of oral administration is related to the lipid moiety [61]. BCV is a nucleotide analog of cytosine and can inhibits the DNA synthesis [61, 62]. This drug currently has been used orally for prophylaxis and treatment of BKV associated disease [63-65]. Garth D. Tylden and colleagues proposed that BCV could be beneficial in prophylactic or preemptive treatment of BKV-HC. Because of its rapid absorption kinetics, intravesicular administration is likely a more effective approach [61, 62].

- *Leflunomide* is an immunosuppressant agent with in vitro antiviral properties against BKV [11, 66-68]. Several studies have utilized Leflunomide as a substitute agent for mycophenolate to treat BKV-HC [11, 69]. Its use is concomitant with a fall in BK viral load. It is not yet clear whether this effect is due to a reduction in immunosuppression or the direct antiviral effect of the drug [11]. Although several undesirable effects comprising hepatitis, hemolysis,

thrombotic microangiopathy, and bone marrow suppression has been reported [11], leflunomide may be a feasible choice without significant toxicity for patient who does not respond to supportive care [69, 70]. In one of the published papers, in which 14 patients were treated with oral leflunomide, 50% complete remission and 35.7% partial remission were reported [70].

- *Quinolone antibiotics* are the important class of broad-spectrum bacteriocidals. Their main structural feature is a bicyclic core structure related to the substance 4 quinolone. Approximately all quinolone antibiotics are fluoroquinolones, which have a fluorine atom in their chemical structure [71]. Quinolones carry inhibitory activity against prokaryotic topoisomerases II (DNA gyrase) and topoisomerase IV. They are effective against a plethora of gram negative and gram positive bacterial infections [29, 71]. Studies have established that fluoroquinolone antibiotics can inhibit BKV replication in vitro [11, 72]. In addition, administration of fluoroquinolones as antibiotic prophylaxis in kidney transplant patients showed fewer BK viremia, further suggesting a possible profit for these antibiotics in preventing BKV replication [11, 73, 74]. Because during asymptomatic phase of the disease, viral replication and viral shedding occur, administration of fluoroquinolones may be able to prevent episodes of severe BKV-HC [11, 29]. Fluoroquinolones prolonged use is associated with the concern of developing antibiotic resistant pathogens especially clostridium difficile diarrhea [29]. The second generation fluoroquinolone *ciprofloxacin*, has been shown that can prevent BK virus replication in vitro, and lead to decrease the BK virus shedding following HSCT [29, 75, 76]. Ashley and colleagues used ciprofloxacin as universal prophylaxis until day 60 after allogeneic HSCT. It seems safe and effective in reducing the occurrence of severe BKV-HC after allogeneic HSCT, with marked concomitant reduction in the risk of bacteremias during the first 100 days after transplantation [29]. *Levofloxacin* which is a third generation quinolone may also have a unique in vivo antiviral activity [71]. Levofloxacin (500 mg/day, orally) may present as an attractive treatment option for achieving complete clinical and molecular response in BKV-HC patients [77]. In addition it helps to avoid utilizing costly and invasive procedures [77].

Overall, current data do not suggest that quinolones presently have a clinically substantial role in the management of BKV related disease [11].

Adoptive cell therapy

Although pharmacological therapies and prophylactic options are available to treat viral infections, they remain limited and ineffective due in part to drug resistance, drug related toxicities and morbidities notably acute kidney injury and myelosuppression [1, 78, 79]. Additionally, prolonged treatment is expensive [1]. For these reasons, a number of authors believe that adoptive cell therapy especially virus-specific T cells (VSTs) might be a logical alternative to conventional treatments for patients with refractory HC [80-85].

VSTs: The preliminary practices of adoptive T cell transfer were based on nonspecific donor lymphocyte infusions (DLIs) which led to restoring antiviral immunity with promising results. However, unmanipulated infused cells provide a lot of alloreactive T lymphocytes resulting in development or exacerbation of GVHD [1, 86]. Consequently, different approaches have been established to increase the purity of virus specific T cells and viral cytotoxicity concomitant with minimizing the alloreactivity. **Table 3** contains different methods used in various articles for generation of VST along with their advantages and disadvantages.

Infusion of adoptive virus specific T cells can prevent viral replication and reestablish antiviral immunity in patients not responding to antiviral therapies. Infusion of adoptive VSTs has been used for almost 30 years. Different methods have been utilized to produce VST against various viruses which reactivated after HSCT and have been associated with remarkable successes. In total among 246 reported patients, 74% responded to the treatment [86]. The estimated response rates are between 50-90%, depending on manufacturing procedures [1]. Overall 85%, 74% and 62% of patients responded to CMV, Adv and EBV specific T cell transfer, respectively [86]. Since VST infusion has been associated with significant improvement in post-transplant complications of these viruses, it is readily applicable to many other viruses include BK and JC polyomaviruses. The

Table 3. Different methods for generation of VST

I. In vitro stimulation and expansion of VST [80, 86, 95, 96]
• Repeated stimulation of donor derived peripheral blood mononuclear cells with antigen presenting cells (APC) pulsed with target antigens. Ultimately expansion of T cells using IL-2.
• Various antigen presenting cells include dendritic cells, monocytes, PHA blasts, B cells and artificial APC can be utilized.
• Antigen sources are comprised of whole virus/viral lysate, whole proteins, viral vectors and peptide/peptide mixtures.
• *Advantage and disadvantage:*
◦ It is the first and most commonly used protocol.
◦ Need relatively a small volume of blood.
◦ Final product containing polyclonal T cells.
◦ This method require a long production time.

II. Direct selection of VST [80, 86, 95, 96]
• Donor white blood cells are isolated in vitro via three different method:
- Peptide-HLA multimers.
- Cytokine-capture method after exposure to viral antigen.
- Based on expression and upregulation of activation molecules on the cell surface such as CD137 (4-1BB) and CD154 (CD40L).
• *Advantage and disadvantage:*
◦ It is a more rapid way to generate VST.
◦ This technique is basically limited to donors with specific immunological memory T cells for the virus.
◦ Large volume of donor blood (100-500 mL) is typically required to reach valuable cell doses.
◦ In vitro activation or expansion lead to exhaustion of T cells.

III. Multivirus-specific T cells [80, 86, 95, 96]
• Generation of VST for each single virus need a separate manufacturing process and it is time and cost consuming. Different practices for the generation of multivirus-specific T cells in one single step have been established.
• This product can be used for patients with multiple refractory viral infections.
• *Advantage and disadvantage:*
◦ Targeting of various viruses in a solitary product.
◦ Challenges comprise production time, cost, and labor.
◦ A potential difficulty is that the most immunodominant antigens will prevent other T cell expansions and diminish the final product of clonal diversity.

IV. Third Party VST [80, 86, 95]
• Manufacturing of donor-derived VST is not always conceivable because of virus seronegative donors or patients undergoing umbilical cord blood (UCB) transplantation. Third-party VST can be utilize for these patients.
• Third-party VST represent an alternative option in patients who don't respond to donor-derived VST because of mutations in viral genome that cannot be recognized by donor T cells.
• This product derived from unmatched donors.
• *Advantage and disadvantage:*
◦ Since it is not from autologous or HLA-matched sources, may increase the risk of GVHD.
◦ It is a partially matched product that could be recognized by the host immune system leading to rejection of VST.
◦ It is a products that could be immediately available in the patients with refractory infections.
◦ It is for "off the shelf" administration that lead to avoid any risky delay in the management of viral disease.

use of VST to treat BKV-HC after HSCT was reported in a single case report [87]. In that study, VST were produced by cytokine capture method and transfused into one patient. The patient showed complete resolution of HC without any complication including GVHD, graft rejection or bystander organ toxicity [87]. In 2014, Papadopoulou and colleagues, generated a multivirus specific T cell product against EBV, CMV, Adv, BKV and HHV6 viruses [88]. The study involved a total of 11 patients, of whom 7 had reactivation of BK virus. After transfusion, 5 and 1 patients achieved complete and partial response, respectively. One patient showed no response to infusion [88]. VST infusion in the setting of BKV-HC is a novel therapeutic technique that is currently in early clinical research. Most of the published papers are case reports and have been performed on a small number of patients. So currently no conclusions can be reached on the efficacy and safety of this approach.

Mesenchymal stromal cells: In recent years, Mesenchymal stromal cells (MSCs) have captured significant interest in regenerative medicine because of their potential immunomodulatory effects, low immunogenicity and wound healing abilities [89, 90]. They can differentiate into various mesenchymal tissues. It has been

shown that they can also reverse tissue toxicity such as hemorrhagic cystitis, because they can directly differentiate into bladder urothelium or indirectly stimulate tissue repair [89, 91]. In this regard in a pilot study, a rapid, significant response was observed after MSC infusion in 8 of 12 patients with severe HC after HSCT [90]. Also, in a retrospective study 5 of 7 HC patients after HSCT responded to this treatment [89]. All studies conducted in this setting have uniformly revealed that it is safe to infuse MSCs in humans with no acute toxicity [89, 90, 92].

Conclusion

BKV-HC considered as one of the major difficulties after HSCT with a prevalence rate of about 40%. It causes significant mortality and morbidity. There is still no standard and approved treatment protocol for BKV-HC and it is according to the local standard operating procedures, depending on the cause and severity. In this review we have divided the therapeutic procedures into 5 categories including conservative therapy, complimentary options, surgical procedures, pharmacological treatments and adoptive cell therapy. Prevention probably is the best treatment of hemorrhagic cystitis. Preventive measures include urine alkalization, hyperhydration, continuous bladder irrigation and the use of MESNA. Most cases of BKV-HC are mild and self-limited and can be treated with conservative therapies or complimentary options, but refractory patients or severe episodes of BKV-HC may require further measures. Currently, there are no specific antiviral drug with strong evidence of clinical efficacy against BKV. The typical clinical method upon identification of BK viremia is gradual reduction of immunosuppression regimen which may increase the risk of acute rejection and exacerbating GVHD. Furthermore its long-term consequence is a higher incidence of chronic rejection. Cidofovir, brincidofovir, leflunomide and quinolone antibiotics have been described to affect the virus replication and can be applied as treatment options. However all studies called for further investigations or a need for high-quality prospective randomized controlled trials to describe the optimal treatment strategies following BKV reactivation. Adoptive cell therapy especially VST therapy is a novel therapeutic method that is currently in early clinical research and can be a logical alternative to conventional treatments. In total, no definitive recommendation is possible for current available treatments because these procedures have only been utilized sporadically in a limit number of patients. Furthermore, a number of treatment options are only experimental and definitely need more effort.

Disclosure of conflict of interest

None.

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