Urological management (medical and surgical) of BK-virus associated haemorrhagic cystitis in children following haematopoietic stem cell transplantation

Nikhil Vasdev1,3*, Angela Davidson1, Christian Harkensee2, Mary Slatter2, Andrew R Gennery2, Ian E Willetts3, Andrew C Thorpe1

1Department of Urology, Freeman Hospital, Newcastle upon Tyne, UK
2Supra-regional Children’s Bone Marrow Transplant Unit (CBMTU), Newcastle General Hospital, Newcastle upon Tyne, UK
3Department of Paediatric Urology, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Received August 19, 2013; Revised September 06, 2013; Accepted September 07, 2013; Published Online September 09, 2013

Original Article

Abstract

Aim: Haemorrhagic cystitis (HC) is uncommon and in its severe form potentially life threatening complication of Haematopoietic stem cell transplantation (HSCT) in children. We present our single centre experience in the urological management of this clinically challenging condition. Patients and Methods: Fourteen patients were diagnosed with BK-Virus HC in our centre. The mean age at diagnosis was 8.8 years (range, 3.2–18.4 years). The mean number of days post-BMT until onset of HC was 20.8 (range, 1–51). While all patients tested urine positive for BKV at the clinical onset of HC, only four patients had viral quantification, with viral loads ranging from 97,000 to >1 billion/ml. 8 patients had clinical HC. Ten patients experienced acute GVHD (grade I: 6 patients, grade II: 3 patients, grade 4: 1 patient). Results: Four patients received medical management for their HC. Treatments included hyperhydration, MESNA, blood and platelet transfusion, premarin and oxybutynin (Table 6). Two patients received both medical and surgical management which included cystoscopy with clot evacuation, bladder irrigation and supra-pubic catheter insertion. One patient received exclusive surgical management. Seven patients were treated conservatively. Conclusion: There is limited available evidence for other potential therapeutic strategies highlighting the need for more research into the pathophysiology of HSCT-associated HC. Commonly used interventions with possible clinical benefit (e.g., cidofovir, ciprofloxacin) still require to be evaluated in multi-centre, high-quality studies. Potential future preventative and therapeutic options, such as modulation of conditioning, immunosuppression and engraftment, new antiviral and anti-inflammatory and less nephrotoxic agents need to be assessed.

Keywords: Haemorrhagic Cystitis; Haemopoietic Stem Cell Transplant; Urological Management; Patient Outcome

Introduction

A significant number of children undergo haematopoietic stem cell transplantation (HSCT) for a range of indications each year. There are various side effects and complications well understood, many of which occur secondary to immunosuppression. Haemorrhagic cystitis (HC) is characterised by haemorrhagic inflammation of bladder mucosa which results in painful micturition associated with haematuria. The clinical course of HC following HSCT can vary from mild and brief (Grade I) to severe, prolonged and life-threatening (Grade IV).1,2

Patients who develop HC following HSCT the onset have either an early or late onset presentation. Early onset occurs within days of transplantation and is associated with associated with conditioning regimen (chemotherapy or irradiation). The late-onset form occurs post-engraftment and is associated with the reactivation of urotropic viruses, principally BK virus, Adenovirus and CMV.3 In current literature, numerous conditioning regimens have been used which in-
clude of the initial use of less toxic conditioning regimens, uroprotective antitoxic agents (e.g. MESNA) or hyperhydration/forced diuresis regimens.

A common theory for the onset of HC following HSCT indicates the role of BK virus reactivation during the time of maximal post-transplant immune suppression in the pathogenesis of late-onset HC. We present our single centre experience in the urological (medical and surgical) management of these patients with this clinically challenging and difficult clinical diagnosis to manage.

Methods and Materials

The aim of this case series was to investigate the cases of all children who underwent HSCT and developed BK-virus HC as a complication, over a 6 year period (2004–2009) at Newcastle General Hospital (NGH). Those who developed BK-virus positive HC following HSCT (n=14) were identified. Notes for all eligible children were sourced and data retrieved on a number of variables: diagnosis necessitating HSCT, date of HSCT, conditioning regimen, donor (whether related and nature of relationship or unrelated), HLA match, Adenovirus and CMV status both pre- and post-HSCT, Graft versus Host Disease (GvHD) prophylaxis, number of days post-HSCT of onset of GvHD, grade of maximal GvHD, treatment of GvHD, number of days post-HSCT of onset of HC, grade of HC, serial BK viral loads in both urine and serum, surgical treatment of HC, medical treatment of HC, serial CD45RA+ counts and eventual outcome. Data was presented on an excel spreadsheet prior to analysis.

Indications for haematopoietic stem cell transplantation (HSCT)

Fourteen patients in total, ten boys and four girls, with a mean age of 8.8 years underwent BMT on our unit between 2004 and 2009 and subsequently developed HC. There were a range of indications. Four had chronic granulomatous disease and two had complex autoimmune disease. The remaining nine patients presented with one of the following: combined immune deficiency, familial haemophagocyticlymphohistocytosis, idiopathic aplastic anaemia, IPEX like complex autoimmune disease, previous Wiskott Aldrich syndrome with chronic EBV, severe congenital neutropenia (HAX1 gene defect), severe periodic syndrome, T-cell acute lymphoblastic lymphoma (Table 1).

Conditioning

Ten different conditioning regimens were used in our patients, almost all of them myeloablative (Table 2). Five received busulfan, cyclophosphamide and camphath. One received each of the following: cyclophosphamide only; busulfan and cyclophosphamide; camphath, fludarabine and cyclophosphamide; camphath, fludarabine and melphalan; camphath, fludarabine and treosulphan; cyclophosphamide, rituximab and busulfan; melphalan, fludarabine and camphath; rabbit ATG, busulfan and cyclophosphamide; treosulfan and cyclophosphamide.

### TABLE 1: Indications for haematopoietic stem cell transplantation (HSCT)

| Diagnosis                                      | Number of Patients | % of Series |
|------------------------------------------------|--------------------|-------------|
| Chronic granulomatous disease                 | 4                  | 26.8        |
| Complex autoimmune disease                    | 2                  | 13.3        |
| Combined immune deficiency                     | 1                  | 6.7         |
| Familial                                       | 1                  | 6.7         |
| haemophagocyticlymphohistocytosis              | 1                  | 6.7         |
| Idiopathic aplastic anaemia                   | 1                  | 6.7         |
| IPEX like complex autoimmune disease          | 1                  | 6.7         |
| Previous Wiskott Aldrich syndrome with chronic EBV | 1              | 6.7         |
| Severe congenital neutropenia (HAX1 gene defect) | 1              | 6.7         |
| Severe periodic syndrome                      | 1                  | 6.7         |
| T-cell acute lymphoblastic lymphoma            | 1                  | 6.7         |

### TABLE 2: Conditioning regimen

| Conditioning Regimen                          | Number of Patients | % of Series |
|------------------------------------------------|--------------------|-------------|
| Busulfan, cyclophosphamide and camphath       | 5                  | 33.5        |
| Cyclophosphamide                              | 1                  | 6.7         |
| Busulfan and cyclophosphamide                 | 1                  | 6.7         |
| Campath, fludarabine and cyclophosphamide     | 1                  | 6.7         |
| Campath, fludarabine and melphalan            | 1                  | 6.7         |
| Campath, fludarabine and treosulphan          | 1                  | 6.7         |
| Cyclophosphamide, rituximab and busulfan      | 1                  | 6.7         |
| Melphalan, fludarabine and camphath           | 1                  | 6.7         |
| Rabbit ATG, busulfan and cyclophosphamide     | 1                  | 6.7         |
| Treosulfan and cyclophosphamide               | 1                  | 6.7         |

### Donor Match

HLA matching was defined as 10/10 match (excluding HLA-DP), where HLA class I was largely low resolution and HLA class II high resolution typed. Except for one HSCT (9/10 match – HLA-A mismatched, unrelated donor) all were 10/10 HLA matched (Table 3).

### TABLE 3: Donor Match

| Donor Match                                | Number of Patients | % of Series |
|--------------------------------------------|--------------------|-------------|
| Unrelated donor (9/10 match)               | 1                  | 6.7         |
| Fully matched sibling donor                 | 4                  | 26.8        |
| Fully matched unrelated donor               | 8                  | 53.6        |
| Fully matched maternal donor               | 1                  | 6.7         |
CMV Status
Ten patients tested negative for CMV both pre and post BMT. Two patients tested negative for CMV pre-BMT and positive for CMV post-BMT. Two patients tested positive for CMV pre-BMT and negative for CMV post-BMT. Two patients had post-transplant adenovirus infection (Table 4).

TABLE 4: CMV Status

| CMV Status Pre- and Post- BMT | Number of Patients | % of Series |
|------------------------------|-------------------|------------|
| Negative pre and post        | 10                | 67         |
| Negative pre, positive post  | 2                 | 13.3       |
| Positive pre, negative post  | 2                 | 13.3       |

Results
The mean age at diagnosis was 8.8 years (range 3.2-18.4 years). The mean number of days post-BMT until onset of HC was 20.8 (range 1 – 51). While all patients tested urine positive for BKV at the clinical onset of HC, only four patients had viral quantification, with viral loads ranging from 97,000 to >1 billion/ml. 8 patients had clinical HC (Table 5). Ten patients experienced acute GVHD (grade I: 6 patients, grade II: 3 patients, grade 4: 1 patient).

TABLE 5: Grade of Hemorrhagic Cystitis

| Grade of HC | No of patients |
|-------------|----------------|
| 0           | 4 (BKV viruria only) |
| 1           | 4              |
| II          | 2              |
| III         | 1              |
| IV          | 3              |

Outcome
Of the fourteen patients two died. One died from multi organ failure, sepsis, on the basis of chronic granulomatous disease, with BMT cited in part II of the death certificate. The other patient died from pulmonary haemorrhage, pneumonia, also with underlying chronic granulomatous disease, with BMT cited in part II of the death certificate. The remaining twelve children survived to discharge and in all cases but one the HC was self-limiting. Eleven went home symptom free and one continued to have occasional macroscopic haematuria on discharge (Table 8).

TABLE 8: Final patient outcome

| Management Strategy | Number of Patients | % of Series |
|---------------------|-------------------|------------|
| Full recovery       | 11                | 73.7       |
| Died                | 2                 | 13.3       |
| Occasional macroscopic haematuria | 1 | 6.7 |

Discussion
Post-engraftment HC tends to present within one month of neutrophil engraftment, resulting in variable disease severity and duration (one week to four months) suggesting multiple contributing risk factors. A three-phase model for post-engraftment HC has been suggested: uroepithelial insult by chemotherapy and radiation providing a permissive environment for virus replication (phase 1), reactivation secondary to immunosuppression (phase 2), and attack of infected uroepithelial cells by donor lymphoid cells upon engraftment, resulting in tissue destruction (phase 3). HLA and immune response gene polymorphisms are also likely to play a role in viral immune responses, as has previously been demonstrated in BK-virus nephropath.

BK-virus
BK-virus is a member of the Polyomaviridae family and was first described in 1971. It was isolated in cell culture from the urine of an asymptomatic immunosuppressed patient. Primary infection with BK-virus usually occurs in childhood and is generally asymptomatic. Therafter, the virus lies latent in the host. BK-virus is urotheliotropic, affecting epithelia of renal calyces, renal pelvis, ureter and urinary bladder. The widespread frequency of BK-virus in children suggests common routes of transmission such as respiratory or faecal spread. Post HSCT HC with BK-virus is widely believed to result from reactivation of latent virus, although new or reinfection has also been postulated. Urinary BK

Copyright © Vasdev et al.
viral load can be quantified by PCR and urinary BK viral load peaks can be correlated with subsequent development of HC.8, 15-17 Urine BK viral loads of >9 x 10^6 copies/ml and blood BK viral load >1 x 10^4 copies/ml are predictive of HC in children, with a higher sensitivity for urine monitoring.6

Incidence of BK-virus associated HCIs varies across different transplant populations, ranging from 3.6% to 20%, according to definition of HC used. A number of prospective and retrospective case series have investigated risk factors for the development of post-engraftment HC, including myeloablative conditioning,18 unrelated donor transplants,19-21 and Adenovirus and CMV infection.22-25 Demographic risk factors include male sex,23, 26 and age >10 years27-30. GvHD is a consistent risk factor in paediatric26, 28, 31, mixed21, 30, 34, and adult20 study cohorts. Busulphan21, 34 and cyclophosphamide28, 35 conditioning which are important risk factors for pre-engraftment HC, seem also to increase risk of post-engraftment HC. Immunosuppressive therapies, including T-cell depletion, ATG, methotrexate, cyclosporin and tacrolimus all lead to a higher incidence of HC.21, 28, 29, 36-38

The management of paediatric patients with post-HSCT HC is difficult. The clinician is confronted with a condition that is potentially life threatening with significant associated morbidity. The recent toxic insult, profound immunosuppression and co-morbidities such as renal impairment severely restrict therapeutic options, however, a recent systematic review supports MESNA and hyperhydration as medical preventative measures and use of recombinant Factor VII in the emergency treatment of acute haemorrhage unresponsive to alternative interventions.6

Medical Urological Management

Hyperhydration with forced diuresis has been studied in the context of pre-engraftment HC caused by the toxic metabolites of cyclophosphamide or ifosfamide. The uroprotective effect of 2-mercaptoethane sodium (MESNA) as a uroprotective antitoxic agent has been investigated as part of high-quality chemotherapy drug trials, and also with regards to efficacy, tolerability and safety compared with hyperhydration5-39 or prophylactic bladder irrigation.40 Results are equivocal, with only one trial reporting an advantage of MESNA over forced diuresis/hyperhydration.4 MESNA and hyperhydration appear to be equally effective in preventing HC, although current studies do not distinguish between early and late onset HC, therefore the protective impact on post-engraftment, BK-virus associated HC cannot clearly be determined.6

Recombinant activated Factor VII (rFVII) has a haemostatic effect leading to formation of thrombin and a haemostatic plug. rFVII was investigated in a randomised, placebo-controlled clinical trial.41 This study enrolled 100 patients aged >12 years with bleeding complications between days 2-180 post-HSCT, 26 of whom had HC. rFVII was given in 3 different doses (40, 80 and 160 μg/kg) as seven single administrations over a 36 hour period, and compared with placebo. Overall, a reduction of the bleeding score at endpoint (38h after first administration) was observed for 80 μg/kg, but not for 160 μg/kg. Six thromboembolic events, including two deaths, were attributed to the study medication. A different dose regimen was used in a prospective case series on patients with HC after high-dose chemotherapy.42 Seven adult patients received initial doses of 80 μg/kg, followed by two further administrations of 120 μg/kg at 3-hour intervals if bleeding persisted. Four patients had a complete, and a further two had partial short lasting responses although bleeding recurred to baseline within hours. Two further small case series report doses of 100 and 400 μg/kg43 and 90 and 270 μg/kg44 to be effective in HC. As a standard rFVII dose of 90 μg/kg costs around £4000 in the UK, treatments according to the above study protocols would cost between £12,000 (for three doses) and £28,000 (for seven doses),45 thereby limiting its use to the most severe of cases.

The evidence for other medical interventions commonly used, and considered ‘conventional’ – systemic cidofovir, oestrogen, hyperbaric oxygen therapy, bladder instillation with alum, formalin or prostaglandins – have been reported to have a weak evidence base, are potentially highly toxic, or both.6

Hyperhydration was employed for three of our patients (21%) with grades II, III and IV HC. MESNA was used for one patient (7%) with grade II HC, and blood and platelet transfusion, premarin and oxybutynin was employed for another patient who also required surgical intervention with bladder irrigation.

Surgical Urological Management

Grade III or IV HC with blood clots often requires surgical intervention. Catheterisation with cystoscopic clot extraction may become necessary, and consideration should be given to continuous bladder irrigation with normal saline for prevention of clots and bladder tamponade, if required.6

HC can occasionally present so severe that it not only fails to respond to conservative measures, but also puts a patient’s life at risk due to uncontrollable haemorrhage or renal failure secondary to complete urinary tract obstruction. Current case literature indicates cystectomy as the final step in the management of severe medically refractory HC.46 Whether a radical or subtotal cystectomy should be performed depends largely on the policy of the unit. Preservation of the bladder neck has been recommended in children because severe HC is improved by cystotomy, temporary urinary diversion and bladder packing.47 Currently, subtotal cystectomy with urethra and bladder neck preservation, allowing subsequent reconstructive continent urological surgery is the preferred option although experience is limited.6
Other surgical management options including use of fibrin glue, selective embolization, and intravesical hydrostatic pressure have been reported to have a weak evidence base or are associated with unacceptable risks.6

Catheterisation and bladder irrigation was only required for two patients (14%) in the current case series population and clot extraction for one patient (7%), indicating that the study unit is adhering to current guidelines in managing post-HSCT HC conservatively where possible, reserving invasive, surgical treatment options only in cases of grade IV HC refractive to simple treatment options.

**Conclusion**

Current guidance on management of post-HSCT HC advocates the following 6:

- Prevention by addressing known risk factors early, employing the best possible donor-recipient matching, using the least toxic conditioning regimen with MESNA/hyperhydration, tight monitoring of viral titres and prompt treatment of re-activation in the peri-transplant period, GvHD prevention and tightly monitored immunosuppression.
- Optimal supportive treatment of manifest HC, with a conservative approach wherever possible and accompanying further management if required: ensuring appropriate hydration and maintenance of renal function, haematological homoeostasis (preserving high platelet counts, appropriate red cell counts and levels of clotting factors), pain relief, catheterisation with cystoscopic clot extraction and continuous bladder irrigation with normal saline for prevention of clots and bladder tamponade, if necessary.
- Early and close collaboration between medical and surgical teams in the management of these patients to coordinate and optimise timing of necessary interventions.
- As post-engraftment HC is by nature a transient condition that resolves with immune reconstitution, the goal is for a conservative approach avoiding measures that may inflict long-term consequences on the patient. Given the low grades of recommendation, any further interventions would have to be considered on an individual basis for a given clinical scenario, carefully balancing benefits and risks.

There is limited available evidence for other potential therapeutic strategies highlighting the need for more research into the pathophysiology of HSCT-associated HC. Commonly used interventions with possible clinical benefit (e.g. cidofovir, ciprofloxacin) still require to be evaluated in multi-centre, high-quality studies. Potential future preventative and therapeutic options, such as modulation of conditioning, immunosuppression and engraftment, new antiviral and anti-inflammatory and less nephrotoxic agents need to be assessed.6

**Conflict of interest**

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**

1. Bedi A, Miller CB, Hanson JL, Goodman S, Ambinder RF, Charache P, Arthur RR, Jones RJ. Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. *J Clin Oncol* 1995; 13: 1103-9.
2. Iwamoto S, Azuma E, Hori H, Hirayama M, Kobayashi M, Komada Y, Nishimori H, Miyahara M. BK virus-associated fatal renal failure following late-onset hemorrhagic cystitis in an unrelated bone marrow transplantation. *Pediatr Hematol Oncol* 2002; 19: 255-61.
3. Leung AY, Mak R, Lie AK, Yuen KY, Cheng VC, Liang R, Kwong YL. Clinicopathological features and risk factors of clinically overt haemorrhagic cystitis complicating bone marrow transplantation. *Bone Marrow Transplant* 2002; 29: 509-13.
4. Hows JM, Mehta A, Ward L, Woods K, Perez R, Gordon MY, Gordon-Smith EC. Comparison of mesna with forced diuresis to prevent cyclophosphamide induced haemorrhagic cystitis in marrow transplantation: a prospective randomised study. *Br J Cancer* 1984; 50: 753-6.
5. Shepherd JD, Pringle LE, Barnett MJ, Klingemann HG, Reece DE, Phillips GL. Mesna versus hyperhydration for the prevention of cyclophosphamide-induced hemorrhagic cystitis in bone marrow transplantation. *J Clin Oncol* 1991; 9: 2016-20.
6. Harkensee C, Vasdev N, Gennery AR, Willetts IE, Taylor C. Prevention and management of BK-virus associated haemorrhagic cystitis in children following haematopoietic stem cell transplantation—a systematic review and evidence-based guidance for clinical management. *Br J Haematol* 2008; 142: 717-31.
7. McCarville MB, Hoefler FA, Gingrich JR, Jenkins JJ 3rd. Imaging findings of hemorrhagic cystitis in pediatric oncology patients. *Pediatr Radiol* 2000; 30: 131-8.
8. Leung AY, Chan MT, Yuen KY, Cheng VC, Chan KH, Wong CL, Liang R, Lie AK, Kwong YL. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis* 2005; 40: 528-37.
9. Bohl DL, Storch GA, Ryschkewitsch C, Gaudreault-Keener M, Schnitzler MA, Major EO, Brennan DC. Donor origin of BK virus in renal
transplantation and role of HLA C7 in susceptibility to sustained BK viremia. Am J Transplant 2005; 5: 2213-21.
10. Ellis D, Shapiro R, Randhawa P, Barnada M, Ferrell R, Vats A. Cytokine gene polymorphisms and risk of BK virus nephropathy in renal transplantation. Am J Transplant 2004; 4: 160-307 (Abstracts1-543).
11. Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet 1971; 1: 1253-7.
12. Bogdanovic G, Priftakis P, Taemmeraes B, Gustafsson A, Flægstad T, Winiarjski J, Dalinas T. Primary BK virus (BKV) infection due to possible BKV transmission during bone marrow transplantation is not the major cause of hemorrhagic cystitis in transplanted children. Pediatr Transplant 1998; 2: 288-93.
13. Dolei A, Pietropaolo V, Gomes E, Di Taranto C, Zicchideddu M, Spanu MA, Lavorino C, Manca M, Degener AM. Polyomavirus persistence in ymphocytes: prevalence in lymphocytes from blood donors and healthy personnel of a blood transfusion centre. J Gen Virol 2000; 81:1967-73.
14. Leung AY, Chan M, Kwong YL. Genotyping of the noncoding control region of BK virus in patients with haemorrhagic cystitis after allogeneic haematopoietic stem cell transplantation. Bone Marrow Transplant 2005; 35: 531-2.
15. Azzi A, Cesaro S, Laszlo D, Zakrzewska K, Ciappi S, De Santis R, Fanci R, Pesavento G, Calore E, Bosi A. Human polyomavirus BK (BKV) load and haemorrhagic cystitis in bone marrow transplantation patients. J Clin Virol 1999; 14: 79-86.
16. Bogdanovic G, Priftakis P, Giraud G, Kuznirn M, Feraldelschi R, Khakhej P, Mellstedt H, Remberger M, Ljungman P, Winiarski J, Dalinas T. Association between a high BK virus load in urine samples of patients with graft-versus-host disease and development of hemorrhagic cystitis from hematopoietic stem cell transplantation. J Clin Microbiol 2004; 42: 5394-6.
17. Leung AY, Suen CK, Lie AK, Liang RH, Yuen KY, Kwong YL. Quantification of polyoma BK viruria in hemorrhagic cystitis complicating bone marrow transplantation. Blood 2001; 98: 1971-8.
18. Giraud G, Bogdanovic G, Priftakis P, Remberger M, Svahn BM, Barkholt L, Ringden O, Winiarjski J, Ljungman P, Dalinas T. The incidence of hemorrhagic cystitis and BK-viruria in allogeneic hematopoietic stem cell recipients according to intensity of the conditioning regimen. Haematologica 2006; 91: 401-4. Erratum in: Haematologica 2009; 94: 1630.
19. Bogdanovic G, Priftakis P, Giraud G, Dalinas T. A related donor and reduced intensity conditioning reduces the risk of development of BK virus-positive haemorrhagic cystitis in allogeneic haematopoietic stem cell-transplanted patients. Anticancer Res 2006; 26: 1311-8.
20. Chakrabarti S, Osman H, Collingham K, Milligan DW. Polyoma viruria following T-cell-depleted allogeneic transplants using Campath-1H: incidence and outcome in relation to graft manipulation, donor type and conditioning. Bone Marrow Transplant 2003; 31: 379-86.
21. Trotman J, Nivison-Smith I, Dodds A. Haemorrhagic cystitis: incidence and risk factors in a transplant population using hyperhydration. Bone Marrow Transplant 1999; 23: 797-801.
22. Akiyama H, Kurosui T, Sakashtia C, Inoue T, Mori Si, Ohash K, Tanikawa S, Sakamaki H, Onozawa Y, Chen Q, Zheng H. Kitamura T. Adenovirus is a key pathogen in hemorrhagic cystitis associated with bone marrow transplantation. Clin Infect Dis 2001; 32: 1325-30.
23. Asano Y, Kanda Y, Ogawa N, Sakata-Yanagimoto M, Nakagawa M, Kawazu M, Goyama S, Kandabashi K, Izutsu K, Imai Y, Hangaishi A, Kurokawa M, Tsujino S, Ogawa S, Aoki K, Chiba S, Motokuta T, Hira H. Male predominance among Japanese adult patients with late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation. Bone Marrow Transplant 2003; 32: 1175-9.
24. Tomonari A, Takahashii S, Ooi J, Fukuno K, Takusugi K, Tsukada N, Konuma T, Ohto N, Uchimaru K, Iseki T, Tojo A, Asano S. Hemorrhagic cystitis in adults after unrelated cord blood transplantation: a single-institution experience in Japan. Int J Hema-tol 2006; 84: 268-71.
25. Yamamoto R, Kusumi E, Kami M, Yuji K, Hamaki S, Saito A, Murasgihe N, Hori A, Kim SW, Makimoto A, Ueyama J, Tanosaki R, Miyakoshi S, Mori S, Morinaga S, Heike Y, Taniguchi S, Masuo S, Takaue Y, Mutou Y. Late hemorrhagic cystitis after reduced-intensity hematopoietic stem cell transplantation (RIST). Bone Marrow Transplant 2003; 32: 1089-95.
26. Hale GA, Rochester RJ, Helson HE, Kranke RA, Gingrich JR, Benaim E, Horwitz EM, Cunningham JM, Tong X, Srivastava DK, Leung WH, Woodard P, Bowman LC, Handgreting R. Hemorrhagic cystitis after allogeneic bone marrow transplantation in children: clinical characteristics and outcome. Biol Blood Marrow Transplant 2003; 9: 698-705.
27. Cesaro S, Brugiolo A, Faraci M, Uderzo C, Rondelli R, Favre C, Zecca M, Garetto G, Dini G, Pillon M, Messina C, Zanesco L, Pession A, Locatelli F. Incidence and treatment of hemorrhagic cystitis in children given hematopoietic stem cell transplantation: a survey from the Italian association of pediatric hematology oncology–bone marrow transplantation group. Bone Marrow Transplant 2003; 32: 925-31.
28. Cheuk DK, Lee TL, Chiang AK, Ha SY, Lau YL, Chan GC. Risk factors and treatment of hemorrhagic cystitis in children who underwent hematopoietic stem cell transplantation. *Transpl Int* 2007; 20: 73-81.

29. Kondo M, Kojima S, Kato K, Matsuyama T. Late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation in children. *Bone Marrow Transplant* 1998; 22: 995-8.

30. Seber A, Shu XO, Defor T, Sencer S, Ramsay N. Risk factors for severe hemorrhagic cystitis following BMT. *Bone Marrow Transplant* 1999; 23: 35-40.

31. Russell SJ, Vowels MR, Vale T. Haemorrhagic cystitis in paediatric bone marrow transplant patients: an association with infective agents, GVHD and prior cyclophosphamide. *Bone Marrow Transplant* 1994; 13: 533-9.

32. El-Zimaity M, Saliba R, Chan K, Shahjahan M, Carrasco A, Khorsheid O, Caldera H, Couriel D, Giralt S, Khouri I, Ippoliti C, Champlin R, de Lima M. Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: donor type matters. *Blood* 2004; 103: 4674-80.

33. Hassan Z, Remberger M, Svenberg P, Elbander M, Karimi M, Andriole Seber A, Shu XO, Defor T, Sencer S, Ramsay N. Late onset hemorrhagic cystitis following hematopoietic stem cell transplantation: donor type matters. *Blood* 2004; 103: 4674-80.

34. Brugieres L, Hartmann O, Travagli JP, Benhamou E, Pico JL, Valteau D, Kalifa C, E, Pico JL, Valteau D, Kalifa C, Claisse JP, Espérou H, Ribaud P, Estrade V, Giralt S, Khouri I, Ippoliti C, Champlin R, de Lima M. Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: donor type matters. *Blood* 2004; 103: 4674-80.

35. Agha I, Brennan DC. BK virus and immunosuppressive agents. *Adv Exp Med Biol* 2006; 577: 174-84.

36. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, Torrence S, Schuessler R, Roby T, Gaudreault-Keener M, Storch GA. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant* 2005; 5: 582-94. Erratum in: *Am J Transplant* 2005; 5: 839.

37. Childs R, Sanchez C, Engler H, Preuss J, Rosenfeld S, Dunbar C, van Rhee F, Plante M, Phang S, Barrett AJ. High incidence of adeno- and polyomavirus-induced hemorrhagic cystitis in bone marrow allotransplantation for hematological malignancy following T cell depletion and cyclosporine. *Bone Marrow Transplant* 1998; 22: 889-93.

38. Wu C, Randhawa P, McCauley J. Transplantation: polyomavirus nephropathy and the risk of specific immunosuppression regimens. *ScientificWorldJournal* 2006; 28: 512-28.

39. Ballen KK, Becker P, Levevbre K, Emmons R, Lee K, Levy W, Stewart FM, Quesenberry P, Lowry P. Safety and cost of hyperhydration for the prevention of hemorrhagic cystitis in bone marrow transplant recipients. *Oncology* 1999; 57: 287-92.

40. Vose JM, Reed EC, Pippert GC, Anderson JR, Bierman PJ, Kessinger A, Spinolo J, Armitage JO. Mesna compared with continuous bladder irrigation as uroprotection during high-dose chemotherapy and transplantation: a randomized trial, *J Clin Oncol* 1993; 11: 1306-10.

41. Pihuschi M, Bacigalupo A, Szer J, von Depka Prondzinski M, Gaspar-Blaudschun B, Hyveled L, Brenner B; F7BMT-1360 Trial Investigators. Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. *J Thromb Haemost* 2005; 3: 1935-44.

42. Ashrani AA, Gabriel DA, Gajewski JL, Jacobs DR Jr, Weisdorf DJ, Key NS. Pilot study to test the efficacy and safety of recombinant factor VII (NovoSeven) in the treatment of refractory hemorrhagic cystitis following high-dose chemotherapy, *Bone Marrow Transplant* 2006; 38: 825-8.

43. Karimi M, Zakerinia M, Khojasteh HN, Ramzi M, Ahmad E. Successful treatment of cyclophosphamide induced intractable hemorrhagic cystitis with recombinant FVIIa (NovoSeven) after allogenic bone marrow transplantation. *J Thromb Haemost* 2004; 2: 1853-5.

44. Blatt J, Gold SH, Wiley JM, Monahan PE, Cooper HC, Harvey D. Off-label use of recombinant factor VIIa in patients following bone marrow transplantation. *Bone Marrow Transplant* 2001; 28: 405-7.

45. BNF, British National Formulary for Children. BMJ Publishing Group Ltd. 2006.

46. Garderet L, Bittencourt H, Sebe P, Kaliski A, Claiss JP, Esperou H, Ribaud P, Estrade V, Gluckman E, Gattegno B. Cystectomy for severe hemorrhagic cystitis in allogeneic stem cell transplant recipients. *Transplantation* 2000; 70: 1807-11.

47. Andriole GL, Yuan JI, Catalona WJ. Cystotomy, temporary urinary diversion and bladder packing in the management of severe cyclophosphamide-induced hemorrhagic cystitis. *J Urol* 1990; 143: 1006-7.