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

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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; Haemopoitic 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 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-

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clude of the initial use of less toxic conditioning regimens, uroprotective antitoxic agents (e.g. MESNA)[4] or hyperhydration/forced dieresis regimens.[5]

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.[6] 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 campath. One received each of the following: cyclophosphamide only; busulfan and cyclophosphamide; campath, fludarabine and cyclophosphamide; campath, fludarabine and melphalen; campath, fludarabine and treosulphan; cyclophosphamide, rituximab and busulfan; melphalan, fludarabine and campath; rabbit ATG, busulfan and cyclophosphamide; treosulfan and cyclophosphamide.

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

Diagnosis	Number of Patients	% ofSeries
Chronic granulomatous disease	4	26.8
Complex autoimmune disease	2	13.3
Combined immune deficiency	1	6.7
Familial 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	% ofSeries
Busulfan, cyclophosphamide and campath	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 campath	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

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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)
I	4
II	2
III	1
IV	3

Grade[6]	Grading System for HC
Grade I	Microscopic haematuria
Grade II	Marcoscopichaematuria
Grade III	Macroscopic haematuria with small clots
Grade IV	Gross haematuria with clots causing urinary tract obstruction requiring instrumentation for clot evacuation

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 (Table 7). Seven patients were treated conservatively.

TABLE 6: Medical Management

Management Strategy	Number of Patients	% of Series
Conservative management	7	46.9
Hyperhydration	4	26.8
MESNA	3	20.1
Blood and/or platelet transfusion	2	13.3
Premarin and oxybutynin	1	6.7

Table 7: Surgical Management

Management Strategy	Number of Patients	% of Series
Cystoscopy and clot evacuation	2	13.3
Heparinised saline bladder irrigation	2	13.3
Supra-pubic catheter insertion	1	6.7

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

	Number of Patients	% of Series
Full recovery	11	73.7
Died	2	13.3
Occassional 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)[7] 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)[8]. 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.[9, 10]

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.[11] Primary infection with BK-virus usually occurs in childhood and is generally asymptomatic. Thereafter, 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 faecalspread.[6] Post HSCT HC with BK-virus is widely believed to result from reactivation of latent virus, although new or reinfection has also been postulated.[9, 12-14] Urinary BK

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viral load can be quantified by PCR and urinary BK viral load peaks have been found to correlate 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 10^3 copies/ml are predictive of HC in children, with a higher sensitivity for urine monitoring.[6]

Incidence of BK-virus associated HCis varied 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 years [27-30]. GvHD is a consistent risk factor in paediatric [26, 28, 31], mixed [21, 30, 34], and adult [20] study cohorts. Busulphan [21, 34] and cyclophosphamide[28, 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 hyperhydration[5, 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/kg [43] and 90 and 270 μg/kg [44] 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]

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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.

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