Hyperbaric oxygen therapy in BKV-associated hemorrhagic cystitis refractory to intravenous and intravesical cidofovir: Case report and review of literature

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Abstract

Hemorrhagic cystitis is a common complication in hematopoietic stem cell transplant recipients. We report here a case of severe BKV-associated hemorrhagic cystitis who did not respond to intravenous cidofovir. Overt hematuria successfully resolved after a few days on hyperbaric oxygen and intravesical instillations of cidofovir, while BK viruria dropped after a few weeks and remained low. We review the literature for therapeutic options in hemorrhagic cystitis and try to explain how hyperbaric oxygen stimulates mucosal repair in the urinary bladder.

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1. Introduction

Hemorrhagic cystitis (HC) is a common complication in both autologous and allogeneic hematopoietic stem cell transplant (HSCT) recipients [1]. Early-onset HC has been associated with cyclophosphamide toxicity and is especially common when prophylaxis with mesna or forced diuresis has not been used. On the contrary, late-onset HC has been associated with some viral infection/reactivations, namely adenovirus type 11 [2,3], human cytomegalovirus (HCMV) [4,5], simian virus 40 [6], and most commonly JC virus (JCV) and BK virus (BKV) [7,8]. The prevalence of asymptomatic BK and JC polyomaviruria increases with age. Approximately 50% of all adult HSCT recipients excrete BKV in urine, yet only about 20% develop HC. In a case series, Bedi et al. found that HC occurred with similar incidence in autologous and allogeneic HSCT recipients, irrespective of prophylaxis with mesna or forced diuresis, and was very strongly correlated with onset of persistent BK viruria [1].

Wide variations exist in BK viruria load in HC patients, although levels of BKV above $10^4$ copies/μl may indicate a risk for HC [9]. No BKV subtype or non-coding control region (NCCR) variant has been definitively associated with HC [10] and studies in pediatric HSCT recipients showed that primary BKV infection is not a major cause of HC [11].

The usual first-line treatment for all other virus-associated HCs is intravenous cidofovir [12], an inhibitor of viral polymerase. While the efficacy of cidofovir (1 mg/kg/day, three times weekly for 3 weeks) against adenovirus-associated HC [13] has been shown in a prospective clinical trial, the efficacy of cidofovir against BKV-associated HC is being systematically investigated only in a retrospective study within the EBMT Infectious Disease Working Party started in 2006 by Cesaro et al. Recently, Savona et al. showed that low-dose cidofovir (1 mg/kg weekly for 4–5 weeks) leads to clinical responses in 84% and a virological responses in 47% of BKV-associated HC [12].
Intravesical cidofovir instillations [14–16] have proved effective in some patients who developed nephrotoxicity after intravenous cidofovir despite probenecid prophylaxis or who experienced no response after multiple courses of intravenous cidofovir.

Since the 1985 report by Weiss et al. [17], hyperbaric oxygen therapy (HBO2) has been successfully used, mainly for early-onset radiation- [9,18–20] or cyclophosphamide [21]-induced HC, but some reports confirmed its utility also against virus-associated late-onset HC [22], with reported response rates ranging from 76% to 100%, independent of prior intravesical chemical instillation [18]. HC is more common in HSCT recipients with inherited clastogenic disorders because of increased susceptibility to reactive oxygen species (ROS): in this setting hyperbaric oxygen therapy is not recommended since it also increases ROS levels [23].

2. Case report

A 20-year old, HCMV seropositive male was diagnosed in March 2006 with acute myeloid leukemia at another Institution. After completing remission with cytarabine and idarubicin induction chemotherapy, he was moved to our Division and on February 2007 he received a HLA-matched, ABO-mismatched, HSCT from a HCMV seronegative unrelated donor after myeloablative conditioning with busulfan, cyclophosphamide and antithymocyte globulin (total reinfused stem cell dose: 4.4 millions CD34+ cells/kg). He successfully engrafted on day +21 and was discharged on day +28. On day +40, while receiving cyclosporine A 325 mg a day p.o., he developed overt hematuria and pollakiuria: BKV in urine was higher than 100 millions per μl at quantitative polymerase chain reaction. The patient received four cycles of intravenous cidofovir (5 mg/kg, associated with probenecid prophylaxis), but BK viruria persistently remained higher than 100 millions per μl. On day +100, while on i.v. cidofovir, he also developed HCMV reactivation (650,000 copies/μl in bone marrow). At that stage his complete blood count was 6000 WBC/μl (CD4+ T lymphocyte count 25/μl; CD4+CD57+ 7.6%; CD8+ 480/μl, CD8+57+ 50%), 6.6 g/dl of hemoglobin and 30,000 platelets/μl, with IgG being 301 mg/dl. Peripheral blood cytokine studies showed raised IL-4 (13.2 pg/ml, normal values 0–5.8) and IL-7 levels (17.3 pg/ml, normal values 0.7–9.2).

Despite complete clearance of HCMV after oral valganciclovir therapy, the patient was admitted again at our Division because of persisting severe HC, which required packed red blood cell and platelet transfusions. Insertion of large urinary catheters and ongoing bladder irrigation were required because of recurrent blood clot retention (as shown by trans-abdominal echography). This classified his HC as Droller grade IV [24]. Since overt hematuria persisted, the patient was given combined intravesical cidofovir instillations (two courses separated by 1 week, consisting each of two infusions of cidofovir 5 mg/kg left in the bladder for 1 h by clamping Foley’s catheter, each infusion 12 h apart). At the end of the second cidofovir course gross hematuria and high urinary BKV loads persisted: after collecting written informed consent, the patient received HBO2. HBO2 was administered in a room with 2 atm absolute air pressure, with 90 min of 100% oxygen breathing via a face mask per day for 7 days. After the fourth day on HBO2, hematuria became microscopic and the patient was discharged, and still remains without hematuria 5 months after procedure. Despite clinical improvement, at the end of HBO2 therapy, BK viruria still was higher than 100,000 copies/μl. Anyway, without any modification in immunosuppressive therapy, 1 month after end of HBO2 therapy, BK viruria dropped to 28 million copies/ml and remains low so far.

3. Discussion

Haemorrhagic cystitis was recognised as a complication of treatment with cyclophosphamide in 1959 [25]: a wide range of agents, including busulfan [26], can predispose to HC. Although the mechanism of injury varies widely and in some cases is known to be due to a specific metabolite, the resultant damage is non-specific [27].

Table 1 summarizes the available treatment options for HC. While the pharmacodynamics of cidofovir against BKV have been described, the mechanisms of action of HBO2 in virus-associated HC is still debated [28]. The proposed mechanism of action of HBO2 is elevation of the oxygen gradient between the damaged, hypoxic urothelium and the normal tissues surrounding it. This stimulates macrophage invasion and production of macrophage-derived proangiogenetic and growth factors. Thus, this is the first available treatment that is potentially disease-modifying. Hader et al. reported a rat model of acrolein-induced cystitis and concluded that exposure to HBO2 increased the amount of intact urothelium [29]. Interestingly, it has been observed that HBO2 induces HSCs mobilization from bone marrow to peripheral blood, suggesting that they might eventually repair the damaged urothelium [30]. Given the time relationship between treatment and negative-activation of BK viruria, we reason that cidofovir (either intravenously or intravesically) had almost no role in the resolution of BK viruria, while we feel the merits could be attributed to improved urothelial function.

Another interesting point is the association of HC with HCMV reactivation. Although some authors suggested that HCMV reactivation could prompt HC [31,32], we feel that a shared denominator for both conditions could be the very low CD4+ T lymphocyte count, which could weaken immune surveillance against normally symbiotic viruses. Furthermore, 50% of CD8+ T lymphocytes in our patients co-expressed CD57, which has been proposed as a marker of immune dysfunction [33].

Also of interest is that fact that HCMV reactivation occurred while our patient was receiving intravenous cidofovir for HC, suggesting that the strain was cidofovir-
Promising, less toxic intravesical agents: [13] indicating that underlying severe immune deficiencies could be a cause of herpes simplex virus stomatitis while being treated with cidofovir, three times weekly for 3 weeks), and two developed herpes genemia while being treated with cidofovir (1 mg/kg/day, administered intramuscularly as single dose in patients with an adequate platelet count [61].

Promising intravenous agents:
1. Cidofovir [14–16]
2. Prostaglandin E2 (PGE2) [44]
3. PGF2α (carboprost tromethamine) [28,45–47]
4. 15-Methyl-PGF2α [48], e-aminocaproic acid [49]
5. Recombinant human granulocyte-macrophage colony-stimulating factor (400 µg for 3 days)[50]
6. Hyaluronic acid [51]

Promising intravenous agents:
1. Valganciclovir [52] for HC due to HCMV
2. Ribavirin [53–55] for HC due to adenovirus
3. Cidofovir [12] for all other virus-associated HCs
4. Vasopressin [56]
5. Coagulation factor XIII concentrates (50IU/kg) [57]
6. Vidarabine (10 mg/kg/day for 5 days) [58–60]. Vidarabine can also be delivered intramuscularly as single dose in patients with an adequate platelet count [61].

Surgical approaches:
1. Sometimes the hemorrhage can be life-threatening and require:
   • Selective vesical artery embolization [62,63]
   • Supraperitoneal cystotomy [64]
   • Open cystectomy [65–67]
   • Laparoscopic cystectomy [68]
2. If the upper urinary tract is involved in HC, ureteral obstruction can develop [69], which may require augmentation ileocystoplasty with ileal ureteral replacement [70].

resistant, a finding which occurs in only 5% of patients [34]. Nagafuji et al. also reported that 4 of 14 patients with adenovirus-associated HC became positive for HCMV antigenemia while being treated with cidofovir (1 mg/kg/day, three times weekly for 3 weeks), and two developed herpes simplex virus stomatitis while being treated with cidofovir, suggesting that underlying severe immune deficiencies could impair the antiviral efficacy of this drug [13].

In summary, we feel that HBO2 worths to be investigated as a non-invasive and effective treatment option for BKV-associated HC.

Conflict of interest statement

This work was supported with institutional funds. We declare that we have no conflicts of interest related to this manuscript.

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References


