

Review Article

Journal of Pharmaceutics and Therapeutics

Pharmacological Options for Viral Induced Hemorrhagic Cystitis Management: A Review of the Literature

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Received: February 28, 2019; Accepted: March 18, 2019; Published: April 04, 2019

Abstract

Background: Viral induced hemorrhagic cystitis (VIHC) is very common among patients who become immunocompromised following organ transplantation. However, there is neither consensus on the standard of care nor clear guidelines to aid in clinical decision making when treating VIHC. This review discusses currently available pharmacologic agents, presents investigational drug therapies, and outlines alternative treatment options that could be effective against VIHC.

Recent findings: Letermovir is a novel antiviral agent approved for CMV prophylaxis in post-hematopoietic stem cell transplantation (HSCT) patients. Although no studies have yet been conducted in patients with VIHC, this new antiviral agent shows promise in preventing emergence of CMV in patients after HSCT. Additionally, newer studies addressing the efficacy of brincidofovir, an experimental drug derived from cidofovir, against CMV infection may provide preliminary evidence for brincidofovir's role in therapy and therefore warrant further investigation.

Conclusion: Polyoma BK virus (BKV), cytomegalovirus (CMV), and adenovirus (ADV) are the primary culprits for HC occurrence in patients undergoing renal transplantation or allogeneic HSCT. CMV-associated HC could be prevented or treated by ganciclovir and valganciclovir because these agents' effectiveness has been clearly established in other non-HC infections related to CMV. ADV-associated HC could be mitigated by brincidofovir and ribavirin, however the high toxicity associated with these agents may be a limiting factor for their use. BKV-associated HC is best managed by cidofovir and leflunomide. Fluoroquinolones are still used in some clinical settings to prevent BK-associated infection, however, their utilization remains controversial. Finally, intravesicular instillation should be preferred in patients who experience toxicities associated with systemic use of antivirals.

Keywords: Hemorrhagic cystitis, Transplantation, BK virus, Cytomegalovirus, Adenovirus

Abbreviations: ADV: Adenovirus; BKV: BK Polyoma Virus; BMT: Bone Marrow Transplantation; CMV: Cytomegalo Virus; HC: Hemorrhagic Cystitis; HSCT: Hematopoietic Stem Cell Transplantation; KT: Kidney Transplantation; NS: Not Statistically Significant.

Introduction

Hemorrhagic cystitis (HC) is characterized by urinary

bladder inflammation and bladder mucosa bleeding. HC can be caused by chemical insults (e.g., chemotherapy),

radiation, or infectious agents such as viruses or parasites [1]. HC can range from microscopic to gross hematuria with clot formation leading to urinary tract obstruction and renal failure [2]. Based on the severity of the hematuria, Droller et al., have developed a grading system for staging HC (Table 1) [3].

Table 1: Hemorrhagic cystitis grading system.

Severity	Symptoms
Grade 1	Microscopic hematuria
Grade 2	Macroscopic hematuria
Grade 3	Macroscopic hematuria with small clots
Grade 4	Gross hematuria with clots causing urinary obstruction requiring instrumentation for clot evacuation and/or causing urinary obstruction

HC caused by viral infection is common in immunocompromised hosts especially those who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) or renal transplantation (RT). Viral-induced hemorrhagic cystitis (VIHC) is a significant cause of morbidity and rarely mortality in these aforementioned patients [4, 5]. Viruses acquired earlier in the patient's life remain latent within cells; and when a patient is given high doses of immunosuppressant, these viruses may reactivate leading to VIHC [6, 7]. In patients with allo-HSCT, the incidence of VIHC has been reported anywhere from 20% to 30% [4]. Viruses that are most commonly implicated in VIHC include polyomavirus hominis 1 (BKV), cytomegalovirus (CMV), and adenovirus (ADV) [8]. Viral infection by any of these viruses can be confirmed using antigen detection, polymerase chain reaction (PCR), virus isolation, or serology [9-11]. The purpose of this article is to review the etiology, standard of care, available treatment modalities, and alternative treatment options for VIHC.

Human ADV are non-enveloped, double-stranded DNA viruses represented by seven species (A through G) which belong to the Adenoviridae family [12,13]. ADV horizontal transmission is frequent and sometimes causes outbreak of pharyngoconjunctival fever even among immunocompetent patients [14,15]. ADV infections may also result in respiratory or gastrointestinal illness [16]. Transplant patients who experience a reactivation of ADV may develop HC [17-23]. The decline in immune function or the use of immunosuppressant agents represents considerable risk factors associated with HC secondary to ADV [24].

BKV are small, non-enveloped, double-stranded DNA viruses which belong to the Papovaviridae family [25,26]. Primary infection of BKV generally occurs during early childhood and can present with a mild fever and upper respiratory infection or may be asymptomatic. The virus infects the majority of the population, with 90% of adults testing seropositive for BKV. Once a patient is exposed to BKV, the virus enters a latent or persistent phase. BKV can remain in various areas of the body but primarily lingers within the urogenital tract [26,27]. Reactivation of latent BKV can occur after transplantation, and replication of the virus can cause many clinical manifestations [25]. Post-transplantation reactivation of BKV occurs early, with additional risk of reactivation in patients who are treated for rejection using high doses of immunosuppressive agents. Pneumonitis, graft nephropathy in post-RT patients, neoplastic diseases, and HC in post-HSCT patients are common manifestations of BKV infection [7,28]. In patients with BKV viremia higher than 104 copies/ml, a higher risk of HC has been noted [29].

CMV is a double-stranded DNA virus which belongs to the beta class of human herpes viruses. Transmission of this virus occurs primarily through bodily fluids or placental transfer [30]. As an opportunistic pathogen, CMV causes both direct damage to organs and indirect harm (including bacterial or fungal infections, cardiovascular events, and acute rejection) in the immunocompromised patient [31]. While a small prospective study confirmed CMV viremia as an independent risk factor for late-onset HC, it is important to note that CMV viruria has not been established as a risk factor [32]. Furthermore, small studies have proposed CMV as a reactivation factor for other viruses, including BKV, but this has yet to be validated [33]. Compared with other causative organisms such as ADV and BKV, the incidence of CMV-associated HC is minimal.

Methods

A search of published articles was conducted using PubMed, Google Scholar, and Cochrane Central Register of Controlled Trials (CENTRAL) in November of 2017 using the MeSH terms "cystitis and virology". Reference selection was performed according to the PRISMA flow chart described in figure 1. Publications were included in this literature review if they were published in the last twenty years, written in the English language, and had an abstract available for review. This search yielded 149 results. The abstracts for all 149 articles were reviewed to identify if treatment options for VIHC were included; if so, the article was included in this review. This

approach yielded 70 articles. References from 3 articles published prior to the year 2000 were added to the final reference list because they contained critical background information on VIHC. This resulted in a total of 73 references. References related to HC treatment options, viral etiology, transplantation type, and therapeutic outcome are summarized in table 2.

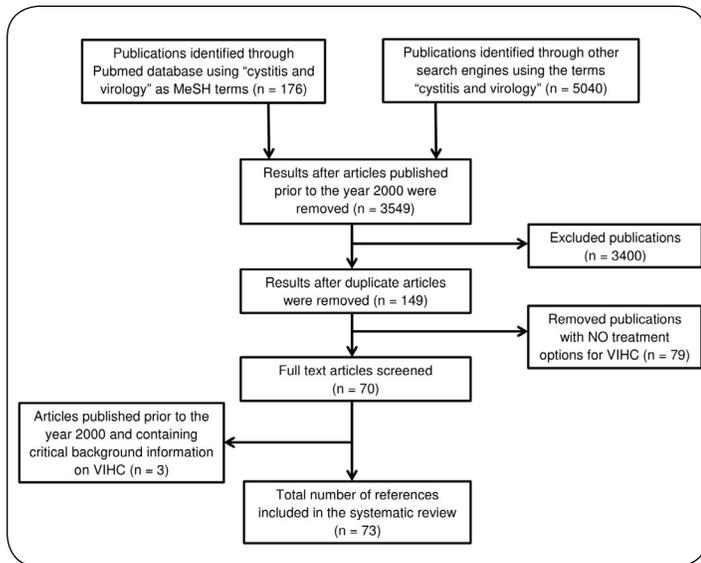


Figure 1: Flow diagram describing the selection of studies included in the systematic review of VIHC treatment.

Results

Prevention & general treatment strategies

The main strategy used to prevent VIHC consists of inhibiting viral replication. The prevention of BKV viral replication can be mitigated by fluoroquinolone antibiotics such as ciprofloxacin and levofloxacin [26]. One study showed that ciprofloxacin regimen could be effective against BKV viral replication in transplant patients [34]. Previously, cidofovir was utilized in BKV-associated HC prophylaxis, however, new evidence suggests that it should be reserved for VIHC treatment exclusively because of its strong myelotoxic and nephrotoxic adverse effects [7]. CMV viral replication can be prevented by ganciclovir, especially in patients undergoing bone marrow transplantation [35]. Consensus on general treatment strategies for HC is limited to supportive and symptomatic measures aimed to control and mitigate the effects of bleeding, the prevention of clot formation or renal obstruction. These measures often include hyperhydration, diuresis, continuous bladder irrigation, analgesia, and blood transfusions [7,24,26,36-38]. Analgesia can range from treatment with topical agents, such as phenazopyridine, to systemic opioid therapy,

such as morphine. Hyperhydration is recommended to help patients achieve a notable increase in the frequency of urination. Additionally, bladder irrigation can be used to prevent clot formation and, therefore, preserve renal function [26,36,37].

Blood transfusions should be considered if a patient is unable to maintain a hematocrit of 25% or greater or has a platelet count less than 50,000 per microliter [26]. In the event that supportive therapies fail or in more severe cases involving substantial bleeding or significant urinary obstruction, surgical approaches via open extraction of bladder clots and cutaneous cystotomy should be considered [39]. Other options include cystoscopy and cauterization [4,7,26,36]. Administration of alum and formalin therapies is considered controversial due to a lack of controlled data, thus appropriateness should be determined by the institution and/or physician [24,26].

Therapeutic agents

Cidofovir: Cidofovir is a cytosine analogue that works by inhibiting DNA polymerase. Cidofovir has shown in vitro and in vivo activity against various viruses, including BKV, ADV, and herpes viruses [40]. Studies and case reports have shown that cidofovir is effective in treating BKV-,CMV-, and ADV-associated HC symptoms and is able to reduce viral DNA levels [40-42].

In 19 transplant patients with BKV-associated HC, the administration of cidofovir 1 mg/kg three times weekly led to clinical improvement in 84% of patients, microbiological response in 47% of patients, and a significant increase in serum creatinine in 26% of patients. Some patients experienced severe nephrotoxicity which was resolved after discontinuation of cidofovir [43]. Nephrotoxicity is a known dose-limiting side effect of cidofovir, which warrants the co-administration of probenecid and normal saline with each dose (package insert).

A case report of a patient with BKV-associated HC and evidence of CMV reactivation identified complete resolution of HC symptoms and significant reduction of viruria with one dose of cidofovir 5 mg/kg, on day-47, day-54, and day-67 post-transplantation. The patient also received estriol to control bleeding, probenecid, and IV hydration with no noted adverse effects [42].

In patients with ADV-associated HC, the use of cidofovir 1 mg/kg/day three times a week for three weeks resulted in clinical improvement and renal clearance of ADV for 71% and 86% of patients, respectively. Co-administration

Table 2: Summary of hemorrhagic cystitis treatment options by viral etiology.

Study	Number of Subjects	Transplantation Type	Antiviral Therapy	Outcome
ADV				
Nagafuji, et al.	14	HSCT	Cidofovir	71% clinical improvement
				86% clearance of viruria
				50% renal toxicity
Gorczyńska, et al.	2	HSCT	Cidofovir	50% symptom resolution
				50% clearance of viremia
Hiwarkar, et al.	16	HSCT	Brincidofovir	81% clearance of viremia
				6% discontinuation due to GI symptoms
Grimely, et al.	48	HSCT	Brincidofovir weekly, Brincidofovir twice weekly, or placebo	No data was statistically significant due to sample size
				Early and consistent declines in viremia in 2x weekly group
				57% diarrhea in twice weekly
				38% diarrhea in once weekly
Ramsay, et al.	3	HSCT	Brincidofovir	67% clinical improvement
				1 patient died
Nakazawa, et al.	1	BMT	Ganciclovir	Complete resolution of symptoms and improvement of viruria
				Neutropenia reported
Yanagisawa, et al.	1	HSCT	Ganciclovir and valganciclovir	Complete resolution of symptoms and improvement of viruria
				Grade II leukopenia reported
				Death unrelated to HC
Miyamura, et al.	9	BMT	IV Ribavirin	33% full resolution
				55% initial partial response with relapse
				5 deaths unrelated to HC
				1 patient death from HC despite therapy
Gavin, et al.	2	Cardiac and BMT	IV Ribavirin	50% symptom resolution
				50% clearance of viruria
				1 non-responder who died secondary to AKI and neutropenia
Abe, et al.	1	HSCT	Oral Ribavirin	Symptom resolution with recurrence of HC at 3 months that was successfully treated with second course of ribavirin
				Myelosuppression
Sahu, et al.	1	HSCT	Ribavirin	Complete symptom resolution
Fanourgiakis et al.	1	BMT	Intravesicularcidofovir	Microbiologic cure
				Symptom resolution
				Improved renal function
				Death unrelated to HC

Study	Number of Subjects	Transplantation Type	Antiviral Therapy	Outcome
BKV				
Savona et al.	19	HSCT	Cidofovir	84% clinical improvement
				47% microbiological response
				26% increase in serum creatinine
Gorczyńska, et al.	19	HSCT	Cidofovir	78% symptom resolution
				100% clearance of viremia
				1 patient died
Wu, et al.	5	HSCT	Leflunomide	100% decreased viremia
				100% symptom improvement
				No side effects noted
Park, et al.	4	HSCT	Leflunomide	50% complete remission
				50% partial response
				1 death unrelated to HC
Chen, et al.	14	HSCT	Leflunomide	50% complete remission
				36% partial remission
				14% no response
Knoll, et al.	154	KT	Levofloxacin	Viruria developed in 29% of levofloxacin treated patients versus 33.3% in patients receiving placebo (NS).
Toptas, et al.	3	HSCT	Levofloxacin	100% symptom resolution
				100% reduction in viruria
Bridges, et al.	1	HSCT	Intravesicularcidofovir	Complete resolution of symptoms and improvement of viruria
				No adverse effects
				Death unrelated to HC
Miodosky, et al.	7	HSCT	Intravesicular sodium hyaluronate	71% clinical improvement
				1 initial response with recurrence
				1 non-responder with death
				No adverse effects
CMV				
Marty, et al.	230	HSCT	Brincidofovir or placebo	100 mg twice weekly decreased incidence of CMV, however 200 mg twice weekly dose did not provide better outcomes, only worse GI side effects
Chemaly, et al.	131	HSCT	Letermovir or placebo	240 mg daily had the greatest prophylactic activity against CMV
				No hematologic toxicity or neurotoxicity were seen
Marty, et al.	565	HSCT	Letermovir or placebo	Lower risk of CMV infection in the letermovir group
				No statistically significant difference in adverse effects compared to placebo
Mixed Infection, BKV with CMV reactivation				
Held, et al.	1	BMT	Cidofovir	Complete resolution of symptoms with significant reduction of viruria

of oral probenecid and intravenous normal saline prevented nephrotoxicity in 50% of patients [40].

In pediatric patients with BKV-, ADV-, and John Cunningham (JC)-associated HC, co-administration of cidofovir and hyperhydration by conjugated estrogens and probenecid resulted in 78.9% of symptoms resolution and 100% viremia clearance [4].

Overall, cidofovir has shown positive effects in the treatment of VIHC, however, future studies could be conducted to determine a standardized dosing regimen for cidofovir and to determine its place in therapy compared to other available agents.

Brincidofovir: This experimental drug is a lipid conjugate of cidofovir with broad-spectrum antiviral activity. It achieves better oral bioavailability and intracellular concentrations than cidofovir [44-46]. It is also active at almost 400-times lower concentration than cidofovir [47]. Unlike cidofovir, brincidofovir appears to be significantly less nephrotoxic [44,46]. In patients who develop brincidofovir-induced nephropathy, kidney function quickly recovers after discontinuation of therapy [44].

In a combined 27-center randomized, placebo-controlled clinical trial involving 230 adult CMV-seropositive transplant patients, 100 mg brincidofovir orally administered twice weekly was effective in reducing the incidence of CMV events compared to placebo. However, dose of 200 mg brincidofovir orally administered twice weekly did not improve efficacy, but rather exacerbated the gastrointestinal adverse effects, notably diarrhea [48].

Brincidofovir 2 mg/kg orally twice weekly following a diagnosis of adenoviremia resulted in total viremia clearance in 83% of patients within four weeks [46].

A case report showed that two ADV infected patients who received 50-100 mg brincidofovir orally twice weekly after initial treatment with cidofovir, survived and tolerated treatment well while a third patient, who received brincidofovir first-line at day 52 post-transplantation, was treated for nineteen days before expiring [49].

The aforementioned studies addressing brincidofovir's efficacy against CMV infection provide preliminary evidence for brincidofovir's role in therapy

and therefore warrant further investigation [44,50-52].

Ganciclovir and Valganciclovir: Ganciclovir competitively inhibits the binding of deoxyguanosine triphosphate to DNA polymerase thus preventing the synthesis of viral DNA (package insert). It should be given as a slow IV infusion to prevent toxicities such as thrombocytopenia, pancytopenia, seizures, acute renal failure, and hepatitis (package insert). Valganciclovir is an oral prodrug of ganciclovir. Both drugs have similar safety and efficacy profiles and may cause hematologic toxicity, especially in renal transplant patients. Both remain first-line options for the prevention and treatment of CMV in transplant patients [30,53,54]. Dosing of both ganciclovir and valganciclovir is safe in patients with normal renal function (package insert) [55]. In addition to renal function, absolute neutrophil count (ANC) should be monitored at least twice weekly in patients receiving ganciclovir or valganciclovir. If neutropenia develops, granulocyte colony-stimulating factor (G-CSF) therapy should be added to the regimen, or the medication should be temporarily discontinued until the ANC rises above 1,000 cells/mm³ for two consecutive days [55]. A case report mentioned an 8-year old pediatric patient who developed dysuria and microscopic hematuria on day 24 post-BMT and who tested positive for the presence of ADV in the urine. The patient was administered ganciclovir 5 mg/kg IV twice-daily regimen for 7 days, followed by 5 mg/kg once daily in addition to supportive care. As a result, urine ADV rapidly declined within 12 days of therapy, and symptoms resolved on day 65 post-BMT [56]. Similarly, the use of ganciclovir followed by valganciclovir in a 9-year-old patient post-HSCT who developed hematuria 12 days after transplantation resulted in symptoms remission and ADV were absent by day 27 post-HSCT and remained undetectable in the blood and urine after stopping therapy [57]. The patient ultimately died 9 months post-HSCT from unrelated causes [57]. These findings suggest that ganciclovir and valganciclovir may be viable drug candidates for the treatment of ADV-associated HC in addition to being the drugs of choice for CMV-associated HC [56,57].

Leflunomide: This drug's pharmacological effect occurs via interference with dihydroorotate dehydrogenase enzyme activity, thus preventing pyrimidine de novo synthesis (package insert). Leflunomide efficacy against BKV-associated HC treatment is well documented [58-60]. In grade 3 or 4 HC pediatric patients, leflunomide significantly decreased BKV viremia and improved symptoms without any major

side effects [60]. In a group of 18 adult allo-HSCT patients diagnosed with BKV-associated HC, four patients required "salvage therapy" with leflunomide due to poor response to supportive care measures [59]. In another group of 14 adult patients, seven obtained complete remission, five achieved partial remission, and two exhibited no response upon treatment with leflunomide [58]. Intolerance to leflunomide varies between gastrointestinal symptoms, such as abdominal bloating and diarrhea, and more severe symptoms, such as neutropenia [58,59]. In cases of neutropenia, a dosage reduction may be warranted in some patients [58].

Letermovir: This medication is a novel antiviral agent that prevents viral replication by inhibiting components of the CMV terminase complex. This agent was recently approved by the FDA for CMV prophylaxis in patients post-HSCT [61,62]. In a phase II multicenter, randomized, double-blind, placebo-controlled study that compared three doses of letermovir for 12 weeks post-HSCT, CMV-seropositive patients were given 60 mg, 120 mg, 240 mg, or placebo orally once daily. The time to onset and failure were dose-dependent outcomes with a significantly lower incidence in the 240 mg group. Additionally, no nephrotoxicity or hematologic toxicity was seen in this study; letermovir had a similar safety profile as the placebo [61]. A second trial was a randomized, double-blind, placebo-controlled phase 3 study using adult patients who had undergone HSCT and were CMV-seropositive with an undetectable viral DNA within 5 days of randomization. Patients who received letermovir 480 mg daily were less likely to develop clinically significant CMV infection compared to placebo by week 24 (37.5% vs. 60.6%, $p < 0.001$) [62]. Although no studies have yet been conducted in patients with HC, this new antiviral agent shows promise in preventing emergence of CMV in patients after HSCT.

Levofloxacin and ciprofloxacin: Levofloxacin antiviral properties result from the inhibition of topoisomerase and the hindrance of helicase activity in the polyoma virus large T antigen [26,63]. Levofloxacin has higher in vivo intracellular activity against atypical bacterial pathogens and may also have higher in vivo antiviral activity compared to ciprofloxacin [64]. Earlier studies showed lower rates of BK viremia after a one-month prophylactic course of a fluoroquinolone antibiotic (either ciprofloxacin or levofloxacin) at one year post-RT [63]. Another study further reported three severe cases of BKV-associated HC which were refractory to supportive measures and ciprofloxacin therapy. Each

of the patients in this study received ciprofloxacin 500 mg orally twice daily for prophylaxis from the day of HSCT until neutrophil engraftment. Within 100 days of HSCT, each patient experienced gross hematuria and was treated with continuous intravesical irrigation, two weeks of ciprofloxacin, and intravesical instillation of risperidone with lack of HC resolution. Oral levofloxacin was then initiated at a dose of 500 mg by mouth daily for eight weeks with monitoring of BKV copies in the urine every 4 weeks. Each patient achieved complete resolution of symptoms and at least a 90% decrease in BKV copies in the urine at the end of the eight weeks of therapy [64]. However, a more recent multicenter, placebo-controlled randomized trial using 154 kidney transplant patients showed that levofloxacin failed to prevent BK viremia within the first year after kidney transplantation [65]. Another study also found no significant difference in treatment outcomes (BK viral load or allograft function) when a one month course of levofloxacin was used in the treatment of BK viremia [66]. In summary, these more recent findings advocate against the use of both levofloxacin and ciprofloxacin in the treatment of post transplantation BKV induced infection.

Ribavirin: Ribavirin is a nucleoside analogue that inhibits the replication of both RNA and DNA viruses. This agent is often utilized in its oral form against hepatitis C virus, in an aerosolized formulation against respiratory syncytial virus, and its IV formulation in cases of hemorrhagic fever and treatment of ADV (package insert) [67]. In patients with ADV-associated HC patients who did not respond to supportive therapy, treatment with IV ribavirin led to full recovery in three of the nine patients. Five patients had an initial partial response with the return of symptoms after completion of therapy but eventually died of complications. The remaining patient died due to disease progression despite ribavirin therapy. Of note, the three patients who made a complete recovery received a transplant from a sibling suggesting to the investigators that a positive correlation exists between ribavirin efficacy and BMT from genetically close donors [68]. When two ADV-associated HC pediatric patients were treated with IV ribavirin, one patient experienced resolution of hematuria within one week with no evidence of ADV in the urine six weeks after discontinuation of ribavirin. The other patient's fever improved, however hematuria continued. Ribavirin treatment was discontinued due to lack of response and the patient eventually died from renal complications [67]. Contrarily to the aforementioned failed case report, a positive outcome was observed in the use of oral ribavirin in a patient who received a HSCT

from an unrelated donor [69]. The patient developed symptoms of HC on day 50 post-HSCT, and ADV was isolated in the urine. Oral ribavirin was initiated at day 94 post-HSCT leading to the patient's fever resolving within 3 days, and other HC-associated symptoms resolved within 14 days. Reduced levels of ADV were seen in the urine for 4 weeks after completion of therapy. Of note, the patient experienced myelosuppression associated with ribavirin therapy. Myelosuppression and hemolysis are well-known adverse effects of ribavirin therapy and may be mitigated with administration of a G-CSF [69]. Another report showed that a 36-year-old post allo-HSCT patient who developed ADV-associated HC was successfully treated with oral ribavirin after for 4 weeks. Symptoms significantly improved within one week of starting therapy and remained negative at follow-up [70]. Ribavirin is an option for the treatment of ADV-associated HC, however further data are needed to determine whether IV or oral formulation result in similar outcomes.

Intravesicular therapies

Intravesicular administration, which consists of direct instillation of the drug into the bladder, limits the amount of systemic adverse effects including nephrotoxicity contrarily to IV formulations. Although, this route is not yet FDA approved for treatment of HC, reports have indicated that patients experience fewer adverse events making this approach a promising alternative [41,71]. In a case report of a 25-year-old male with BKV-associated HC post allo-HSCT, intravesicular cidofovir was initiated after failed supportive therapy [41]. Cidofovir 5 mg/kg in 60mL of normal saline was administered intravesicularly over 15 minutes, allowed to dwell for one hour, and then drained. After a second instillation was performed one week later, hematuria significantly decreased and the patient no longer required transfusion support. No adverse effects, including nephrotoxicity were observed. The patient was discharged from the hospital but ultimately died from relapsed leukemia [41]. In another report, the intravesicular administration of cidofovir to a 34-year-old male post-BMT suffering from grade 4 ADV-associated HC lead to hematuria resolution and non-detection of ADV cultures and antigen a few days later. Unfortunately, two weeks after cidofovir therapy was started, the patient developed sepsis and died of multi-organ failure unrelated to ADV [71].

Hyaluronic acid, also known as sodium hyaluronate in salt form, is a glycosaminoglycan found on bladder mucosa which prevents uro-epithelial damage by forming a protective barrier [72, 73]. Additionally, it has

been hypothesized that hyaluronic acid may affect viral replication of BKV [72]. In a small report of seven post-HSCT adult patients, intravesicular sodium hyaluronate was administered as an adjunct to standard treatment of hydration, diuresis, bladder irrigation and transfusion support in patients diagnosed with BKV-associated HC. Patients received 40 mg of sodium hyaluronate by intravesicular administration, and the solution was retained within the bladder for a minimum of 20 minutes. The regimen was repeated 7 days later in patients who did not respond to the initial therapy. Intravesicular sodium hyaluronate was effective in five of the seven patients without significant adverse effects. One of the patients who did not respond to therapy died, and another patient had an initial response followed by post-treatment recurrence of HC [72]. Finally, a pediatric case report demonstrated efficacy using the same dosing regimen with a dwell time of one hour [73]. Additional research is necessary to further define the role of hyaluronic acid in the treatment of HC.

Discussion

Figure 2 summarizes the major antiviral agents used to treat the underlying virus responsible for HC. Currently ganciclovir and valganciclovir are the agents most often utilized in the prevention and treatment of CMV-associated HC as these agents are well studied in other CMV infections. Brincidofovir and letermovir may play a role in the treatment CMV in the future, however the former agent is not yet FDA approved. Cidofovir and ribavirin have successfully treated ADV-associated HC, however toxicities may be a limiting factor of their use. Ganciclovir and brincidofovir have limited data to support their use in ADV-associated HC, however these options may be alternatives in the event that patients cannot tolerate commonly used agents. While evidence supporting the use of leflunomide in the prevention and treatment BKV-associated HC, fluoroquinolones such as levofloxacin and ciprofloxacin have shown controversial results. A recent multicenter placebo-control trial found that the use of levofloxacin was not effective in preventing posttransplantation BK virus infection in kidney transplant patients [65]. Cidofovir and brincidofovir may be used as alternatives, however less data exist to support their use at this time. An alternative route of administration, such as intravesicular instillation, may be an option in patients who may be prone to or experience toxicities associated with systemic use of antivirals. Our thorough evaluation of the literature provides preliminary data to help establish consensus in clinical decision making when treating HC.

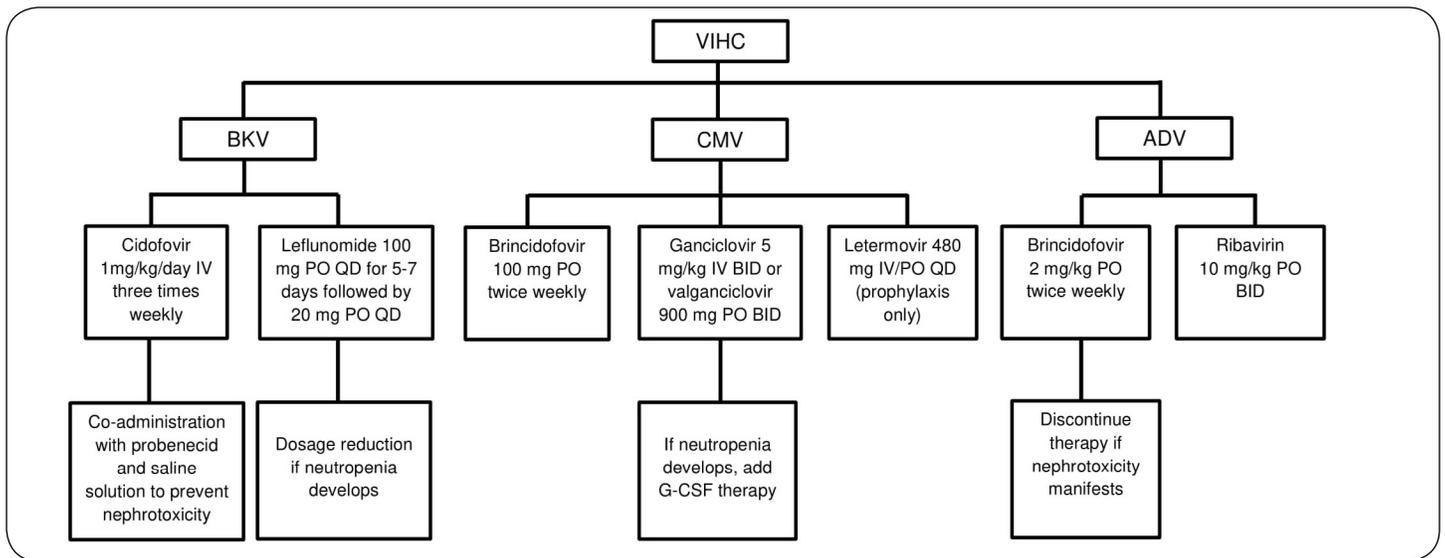


Figure 2: Summary of pharmacological agents used in the treatment and prophylaxis of VIHC.

Limitations

The limitations of our study reside in the fact that most data reported include complicated patients who also have comorbidities post-transplantation conditions. Therefore it is often difficult to discern which interventions are most effective in treating HC. There is also a lack of prospective studies, and to date no large studies directly comparing agents are available.

Conclusion

VIHC is a significant cause of morbidity in patients who have undergone allo-HSCT or other forms of transplantation. Patients may present with various degrees of hematuria, all of which require supportive care measures including hyperhydration, continuous bladder irrigation, blood transfusions, and analgesia. Although several antiviral agents are available to target specific underlying viral etiologies, further studies are needed to determine the place in therapy for each available agent used to prevent and treat VIHC.

Declarations

Ethics approval and consent to participate

N/A

Consent for publication

The authors give consent for publication.

Availability of data and material

N/A

Competing interests

The authors declare they have no conflict of interest.

Funding

N/A

Author's contributions

All authors contributed equally to the manuscript.

Acknowledgment

The authors would like to thank Kerri Bergrin, PharmD for her initial compilation of references included in this manuscript.

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