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Haemorrhagic cystitis, preventive and treatment interventions in patients undergoing haematopoietic stem cell transplantation: A scoping review

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ABSTRACT

Purpose: to map (a) methodological features, (b) Haemorrhagic Cystitis (HC) preventive and treatment interventions scrutinized to date, (c) outcomes measured, and (d) trends in effectiveness as documented among Haematopoietic Stem Cell Transplanted (HSCT) adults.

Methods: A scoping review was performed in 2018. Medline, CINAHL, and Cochrane Systematic Reviews databases were researched using "haemorrhagic cystitis", "prevention", "treatment", "prevent*" and "treat*" as search terms. Handsearching was also performed. Clinical trials, randomized controlled trials, comparative and observational studies, reviews, systematic reviews and meta-analyses published in English and concerning adults were all included.

Results: Fifteen primary studies, mainly monocentric, retrospective and with a sample size <200, were identified. Seven focused on preventive (mainly continuous bladder irrigation and mesna) and eight on treatment interventions (mainly intravenous and intravesical cidofovir). The onset of micro and macrohaematuria and the clinical resolution of HC were the main measured outcomes. Positive effectiveness trends were apparent for mesna and cidofovir.

Conclusions: In HC prevention and treatment, published primary studies are sparse and further research is required with larger, multicenter, and longitudinal designs conducted at international levels, with standardized methods, interventions, outcome measures, and reported data.

1. Introduction

In 2017, around 172,910 new cases of haemolymphopoietic tumours have been diagnosed in the US (Siegel et al., 2017). In patients whose disease is not responsive to conventional therapies, Haematopoietic Stem Cell Transplantation (HSCT) has been reported as the last therapeutic choice. According to recent data, 45,418 HSCTs have been performed by 683 teams across 63 European and affiliated countries. Of these, 18,281 (40%) have been allogeneic and 27,137 (60%) autologous (Annual Report of the European Society for Blood and Marrow Transplantation [EBMT], 2018). In these patients, Haemorrhagic Cystitis (HC) has been documented as a severe complication causing bleeding from the bladder mucosa and symptoms ranging from microhaematuria to pain, dysuria, severe haematuria and potential retention of clots and, ultimately, renal failure (Gaziev et al., 2010). The incidence of HC has been reported to range from 18% to 40% (Gonella et al., 2015; Hadjibabaie et al., 2008; Tsuboi et al., 2003), reaching severe grades in 4–8% of cases (Lee et al., 2003; Xu et al., 2007).

HC is defined as Early Onset Haemorrhagic Cystitis (EOHC) when it occurs within 48 h, or Late Onset Haemorrhagic Cystitis (LOHC) when it occurs after 48 h from the conditioning regime (Russel et al., 1994). EOHC has been associated with a conditioning regime involving alkylating agents such as oxazafosforine (cyclophosphamide [CY] and ifosfamide) and busulfan (Lee et al., 2003). The aetiology of LOHC is less well understood and is associated with the reactivation of some viruses (Adenovirus [ADV] and BK virus [BKV] Cesaro et al., 2013; Sakurada et al., 2016), acute Graft Versus Host Disease (GVHD) (Federoff, 2008; Hadjibabaie et al., 2008), the use of high doses of antithymocyte globulins, the type of HSCT performed and the compatibility between the donor and the recipient (Gonella et al., 2015; Xu et al., 2007).

At the patient level, HC has been reported to increase the in-hospital stay and the risk of mortality (Cesaro et al., 2013; Tsuboi et al., 2003). Therefore, with the aim of preventing and managing this complication, various studies have been performed to date, including the pediatric population.

Among the preventive interventions, studies have mostly focused on decreasing the concentration of acrolein and its contact time with the

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urothelium for example by administering Continuous Bladder Irrigation (CBI) (Gonella et al., 2015; Hadjibabaie et al., 2008; Vose et al., 1993). Urine alkalinization, hyperhydration (Cesaro et al., 2013; Gonella et al., 2015) and forced diuresis (Bedi et al., 1995) have also been documented. Moreover, 2-mercaptoethane sodium sulphonate (or mesna), a widely used pharmacological agent, has been tested for its capacity to react with acrolein, making it less toxic at the bladder level, in addition to CBI, hydration and urine alkalinization (Gonella et al., 2015; Hadjibabaie et al., 2008).

In terms of treatments, antivirals have been widely used in HC associated with BK virus (Miyamura et al., 2000; Paduch, 2007; Philippe et al., 2016). Prostaglandins have also been studied for more than 20 years, with the conclusion that they are safe and inexpensive treatments, especially in refractory HC (Ippoliti et al., 1995; Laszlo et al., 1995). Tranexamic and e-aminocaproic acid as haemostatic agents, intravesical instillations of formalin and alum (Roskopf et al., 2002), hyaluronic acid (Miodosky et al., 2006) and fibrin glue (Tirindelli et al., 2009) have also been studied over the years. Recently, studies have suggested the use of specific T-BKV cells as the best therapeutic option to treat HC and to minimize the risks of GVHD (Mani et al., 2014; Tzannou et al., 2017) while Hyperbaric Oxygen Therapy has been suggested for severe grades of HC (Mackey, 2012; Philippe et al., 2016). Cystoscopy with clot evacuation, cautery and surgical interventions (including radical cystectomies) has also been reported in patients at risk of death (Dropulic and Jones, 2008; Ippoliti et al., 1995). Alongside these treatments, supportive interventions aimed at providing comfort to patients have also been studied (Ippoliti et al., 1995; Philippe et al., 2016; Pihusch et al., 2005).

Various reviews (for example, Mackey, 2012; Philippe et al., 2016) have been conducted to date particularly on HC treatments in HSCT adults; however, no systematic review has been performed and no gold standards have been established in the field. Furthermore, to our best knowledge, no reviews have been performed on the preventive interventions which are crucial in the clinical practice of nurses. Therefore, with the aim to support the development of more focused lines of research on both HC prevention and treatment the intent of our study was to map:

(a) the methodological features of research performed to date in the field,
(b) the preventive and treatment interventions scrutinized,
(c) the outcomes measured to establish their effectiveness, and
(d) the trends in effectiveness as documented in studies including HSCT adult population with HC.

The HSCT population was considered given its high risk of developing HC due to different factors, such as the conditioning regime (Lee et al., 2003), the reactivation of some viruses (Cesaro et al., 2013; Sakurada et al., 2016), the acute GVHD (Federoff, 2008; Hadjibabaie et al., 2008), and the use of high doses of anti-thymocyte globulins (Gonella et al., 2015; Xu et al., 2007) which are all less probable in other populations, thus characterizing those receiving HSCT as unique.

2. Methods

2.1. Study design

A scoping review was performed in 2017 and updated on June 15th, 2018, following the procedure defined by Levac et al. (2010): (a) identification of the research question(s), (b) identification of relevant studies, (c) selection of studies for inclusion, (d) collection of data, and (e) collation, summary, and reporting of the findings. Specifically, the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR, Tricco et al., 2018) Checklist was followed to report the process and the findings of the Scoping review as reported in the Supplementary Table 1.

2.2. Research questions

According to the study aims, the research questions were the following:

(a) Which studies have investigated interventions aimed at preventing or managing HC in adult HSCT patients?
(b) Which preventive and treatment interventions have been studied in the field?
(c) Which outcomes have been measured in the available studies, and
(d) Which trends in effectiveness of interventions tested have been documented to date?

2.3. Relevant studies

The Medline and Current Index to Nursing and Allied Health Literature (CINAHL) databases, and Cochrane Database of Systematic Reviews (CDSR) were searched using free text-words given that the Mesh Term “Haemorrhagic Cystitis” has not been established to date. The following text-words were used: “haemorrhagic cystitis”, “prevention”, “treatment”, “prevent*” and “treat*” combined by using the Boolean operators “AND” and “OR”. Specifically, in Medline database, the search string was: “haemorrhagic cystitis AND (prevention OR treatment)” and “haemorrhagic cystitis AND (prevent* OR treat*)”; moreover, in order to include a wider amount of studies, the keyword “Hemorrhagic cystitis” was used for CINAHL and for CDSR database. Handsearching was also performed.

2.4. Study selection

Studies satisfying the following inclusion criteria were selected: (a) clinical trials, randomized controlled trials (RCTs), comparative and observational studies including also case series, reviews, systematic reviews and meta-analyses; (b) published in English; and (c) concerning post HSCT adults (19 + years). Therefore, single case reports, comments, letters, preclinical studies, as well as studies including patients not undergoing HSCT or including the paediatric population were all excluded.

Two researchers (CV, MV) screened the titles and abstracts against the inclusion criteria independently in the first stage and then reaching a consensus on eligible studies. The full text of articles that met the inclusion criteria was retrieved and reviewed for their final inclusion by the same researchers (CV, MV) independently, and then with common agreement. Furthermore, in the four reviews emerged (Lynch and Kajon, 2016; Mackey, 2012; Philippe et al., 2016; Satyanarayana et al., 2014) primary studies non consistent with the inclusion criteria were removed. For example, four out of five studies from the Mackey's review (2012) (Bridges et al., 2006; Focosi et al., 2009; Eisen et al., 2009; Rao et al., 2009) were removed as the first two were case reports, the third focused on paediatric patients and the fourth was a letter. Moreover, one study (Ganguly et al., 2010) included in two reviews (Mackey, 2012; Philippe et al., 2016) was considered as a unique study.

A total of 11 sources were included: one was split according to its double nature as a retrospective and a review study (Philippe et al., 2016). Therefore, 15 primary studies were included: (a) eight of them were primary studies, and (b) seven were retrieved inside of reviews.

The full process is reported in Fig. 1 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

2.5. Data extraction and synthesis

The following data was extracted:

(a) For the first and second research questions: publication (authors, year, country), aim(s), study design, units involved (monocentric

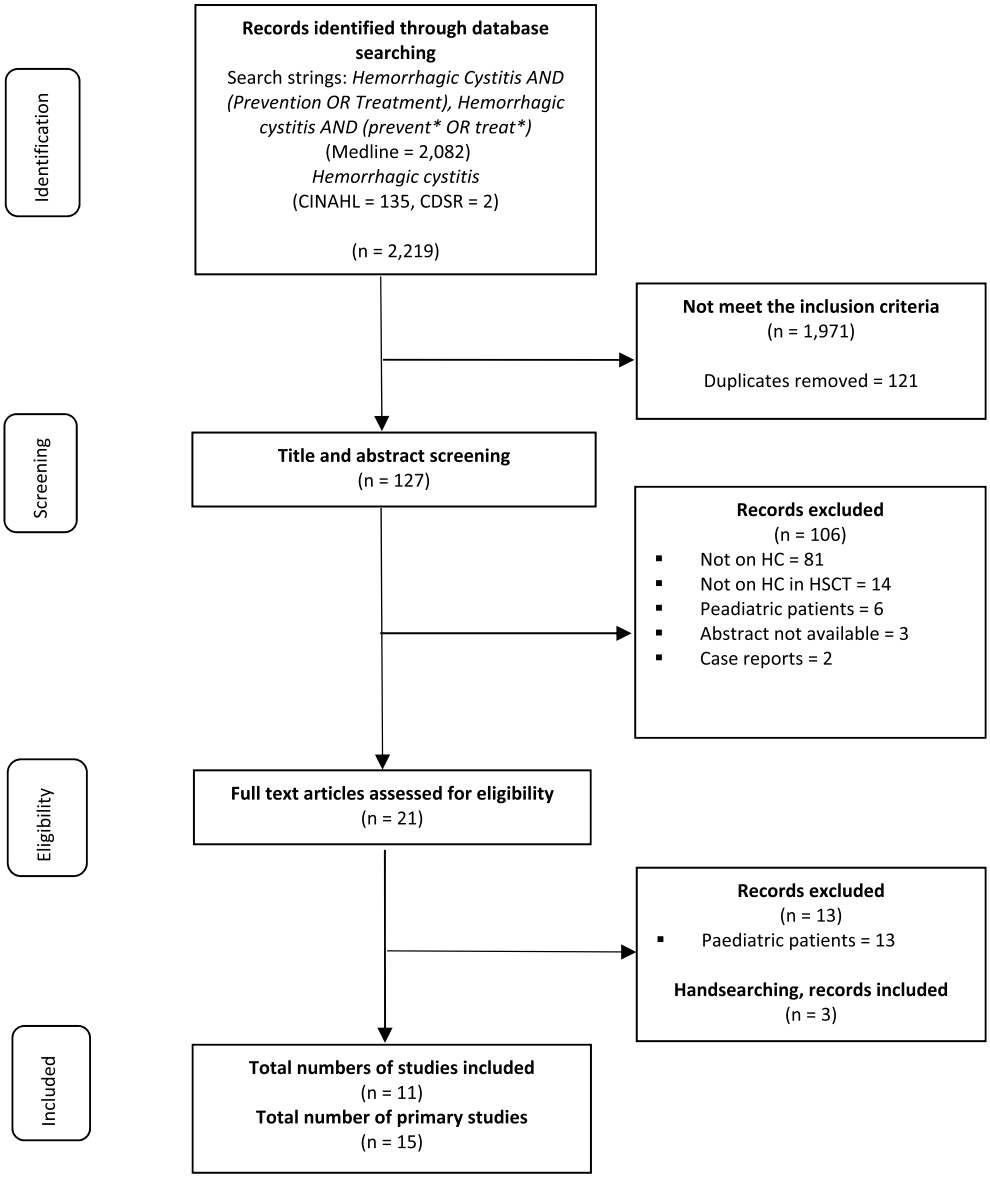

Fig. 1. Flow-diagram of the review process according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009)
Abbreviations: CINAHL: Current Index to Nursing and Allied Health Literature; CDSR: Cochrane Database of Systematic Reviews databases; HC: Haemorrhagic Cystitis. HSCT: haematopoietic stem cells transplanted.

vs. no) and study duration, population (sample size, age, gender) and preventive or treatment intervention(s) performed both in the exposed and in the control group;

(b) For the third research question: the outcome(s) measured (for example, grading of HC, time of appearance of HC, incidence of HC);

(c) For the fourth research question: trend in effectiveness as reported by studies for HC preventive and treatment interventions.

Two researchers (CV, MV) read the full text carefully and then extracted data independently before agreeing on them.

Given the aim of the scoping review, the quality of the studies included was not assessed (Levac et al., 2010).

3. Results

3.1. Study methodological features

As reported in Table 1, eight primary studies, and four reviews (Lynch and Kajon, 2016; Mackey, 2012; Philippe et al., 2016; Satyanarayana et al., 2014) were retrieved. Specifically, the review of Philippe et al. (2016) was based upon two studies, a retrospective primary study and a literature review: according to its double nature, the study was reported twice.

Nine studies were conducted in the USA (Bedi et al., 1995; Breitz et al., 2003; Ganguly et al., 2010; Giralt et al., 2003; Ippoliti et al., 1995; La Rosa et al., 2001; Miller et al., 2011; Savona et al., 2007; Vose et al., 1993), two in France (Gilis et al., 2014; Philippe et al., 2016), and the remaining in Italy (Gonella et al., 2015), Iran (Hadjibabaie et al., 2008), Korea (Lee et al., 2015) and Japan (Kawakami et al., 1997), respectively. Only three studies were multicentric in nature (Breitz et al., 2003; Giralt et al., 2003; Gonella et al., 2015).

The majority of studies were retrospective in nature (Ganguly et al., 2010; Gilis et al., 2014; Gonella et al., 2015; La Rosa et al., 2001; Lee et al., 2015; Philippe et al., 2016; Savona et al., 2007); three were Phase I/II trials (Breitz et al., 2003; Giralt et al., 2003; Ippoliti et al., 1995); two were RCTs (Bedi et al., 1995; Vose et al., 1993), and the remaining were quasi-experimental (Hadjibabaie et al., 2008), perspective (case series, Kawakami et al., 1997) and both retrospective and prospective

Table 1
Main features of the included studies.

Methods						Findings		
Author, Country	Design, and duration	Population	Specific risk factors	Experimental (n)	Comparison (n)	Measures	Collateral effects	Linking evidence to practice
Preventive Interventions								
Bedi et al. (1995) USA	Design: RCT Monocentric Duration: August, 1991 – June, 1993	E = 71 A Age: 40 years Gender M = 40 (56.3%) C = 76 A Age: 38 years Gender M = 47 (61.8%)	CY/TBI = 54 (36.7%) BU/CY = 63 (42.8%) BU/CY/etoposide = 30 (20.4%) BK viruria = 50 (52.6%)	Mesna: 60 mg/kg/day = 120% dose of CY, in 5 intravenous doses 30 min before CY and 3, 6, 9 and 12 h after each dose of CY Intravenous hydration: 2 ml/kg/h from 12 h before CY and continued until 24 h after last dose of CY Intravenous furosemide: if urine output < 1.5 ml/kg/h in 4 h or urine specific gravity > 1.010 or increased body weight > 1 kg	Mesna: - Intravenous hydration: 4 ml/kg/h from 12 h before infusion of CY and continued until 24 h after last dose of CY. Rate incrementation to 5 ml/kg/h if urine output < 3 ml/kg/h in 4 h or urine specific gravity >1.010 Intravenous furosemide: if increased body weight > 1 kg	HC grading: II–III (Bedi et al., 1985) Time of appearance: 26 (14–126) days post-HSCT E = 19 (26.8%) C = 18 (23.7%) (p = 0.41) Risk of HC: 0% in patients without BK viruria vs. 63% in patients with persistent BK viruria	Not reported	Mesna and forced diuresis are equally effective in the prevention of early-onset HC due to the urotoxicity of CY metabolites. It is also necessary to prevent or eliminate viruria in BKV-positive patients because this is an important risk factor for HC
Breitz et al. (2003) USA	Design: Phase I/II trial Multicentre Duration: -	E = 29 Age: - Gender: - C = 54 Age: - Gender: -	Escalating doses of ^{166}Ho-DOTMP, MEL = 83 (100%) TBI = 25 (30.1%)	CBI: administered	CBI: - Frequent voiding and hydration	HC grading: I–III (NCI CTCAE) Time of appearance: > 28 days post-HSCT E = 2 (6.9%) C = 25 (46.3%)	Not reported	CBI must be used in patients for at least 6 hours following therapy dose with ^{166}Ho-DOTMP, MEL and TBI (< 40 Gy)
Giralt et al. (2003) USA	Design: Phase I/II trial Multicentre Duration: June, 1998 – April, 2000	E = 32 C = 51 A Age: 54 (36–71) years Gender M = 50 (60.2%)	Escalating doses of ^{166}Ho-DOTMP, MEL = 83 (100%) TBI = 25 (30.1%)	CBI: at 200 ml/h prior to and until the day following ^{166}Ho-DOTMP	CBI: - Intravenously hydration: at 200 ml/h of dextrose 5% and half normal saline solution Forced diuresis and frequent voiding: every 2 hours	HC grading: II–III (NCI CTCAE) Time of appearance: 1–45 months post-HSCT E = 2 (6.9%) C = 25 (46.9%)	Not reported	Bladder exposure to ^{166}Ho-DOTMP can be minimized by using CBI
Gonella et al. (2015) Italy	Design: retrospective Multicentre Duration: January, 2006 – December, 2008	E = 51 C = 107 A Age: 41.9, CI 95% [40.1, 43.8] years Gender M = 92 (58.2%)	BU-CY = 94 (59.5%) CY-THIO = 53 (33.5%) CY-TBI = 8 (5.0%) CY = 3 (1.9%)	CBI: 300 ml/h of saline on the day of the 1st dose of CY until 48–72 h after last drug dose Hyperhydration: 2500 ml/day (= 157) Mesna: median 3863 ml/day (=157) Diuresis alkalinization: 980 ml/day of 1.4% $NaHCO_3^-$ (=147) Antibiotic therapy with fluoroquinolones (=139) Supportive measures when HC has developed: catheterization (=9), CBI (=4)	CBI: -	HC grading: I–III (Leung et al., 2002) Time of appearance: < 21 days post-HSCT E = 10 (20%) C = 21 (20%) (p = 0.73)	Discomfort and UTI (E)	Hyperhydration associated with diuresis alkalinization and mesna represents the current gold standard for preventing EOHC in HSCT regimens. Preventive urethral catheterization and CBI showed conflicting data. Nursing practice should consider benefits and harms of preventive catheterization and CBI

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Table 1 (*continued*)

Methods						Findings		
Author, Country	Design, and duration	Population	Specific risk factors	Experimental (n)	Comparison (n)	Measures	Collateral effects	Linking evidence to practice
Hadjibabaie et al. (2008) Iran	Design: Non-randomized controlled trial Monocentric Duration: May, 2006 – (-)	E= 40 A Age: 27 (SD 9.4) years Gender M= 28 (70%) C= 40 A Age: 28 (SD 9.5) years Gender M= 25 (62.5%)	BU-CY= 75 (93.7%) ATG-CY= 4 (5%) FLU-CY= 1 (1.25%) Acute GVHD= 21 (26.2%) CMV infection= 23 (28.7%)	CBI: normal saline at 300 ml/h, 12 h before the 1st dose of CY until 48 h after the last dose of CY Intravenous mesna: 60% dose of CY before CY and a 40% dose of CY every 6 h for a total of 3 doses Hydration: dextrose water or normal saline containing KCl Alkalinization with $NaCOH_3^-$: before and during CY	CBI: - Intravenous mesna: 60% dose of CY before CY and a 40% dose of CY every 6 h for a total of 3 doses Hydration: dextrose water or normal saline containing KCl Alkalinization with $NaCOH_3^-$: before and during CY	HC grading: II–V (Droller et al., 1982) Time of appearance: E= 8.5 (SD 11.9) days post-HSCT C= 31.2 (SD 23.8) days post-HSCT EOHC: E= 13 (32.5%) C= 20 (50%) ($p=0.11$) LOHC: E= 4 (7.7%) C= 18 (45%) ($p=0.009$) Duration: E= 10 (SD 5.4) days C= 18 (SD 12.3) days ($p=0.02$) UTI: E= 13 (32.5%) C= 8 (20.0%) ($p=0.20$)	Discomfort relating to catheterization (E)	CBI added to mesna, hydration, and alkalinization regimens is well tolerated, decreases the complications of HC and may be useful in HSCT patients. Furthermore, they can reduce incidence of HC and duration of hospitalization. CBI appears to be a safe and well-tolerated regimen
Satyanarayana et al. (2014)§ USA	Design: review [1] Miller et al. (2011), retro-prospective USA	[1] E= 44 A Age: 55 (44-62) years Gender M= 29 (66%) [1] C= 48 A Age: 44 (31-56) years Gender M= 28 (58%)	[1] MEL and/or TBI and/or BU= 43 (39.6%) ATG= 1 (1.1%) BK viruria= 92 (100.0%) GVHD= 38 (41.3%)	[1] Orally ciprofloxacin 500 mg every 12 hours from the day of HSCT until neutrophil engraftment (typically, the third consecutive day of neutrophils >500/mm^3) [1] Orally ciprofloxacin 500 mg every 12 hours from the day of HSCT until day 60 after HSCT	[1] Orally ciprofloxacin: -	[1] HC grading: III-IV (Leung et al., 2002) [1] Time of appearance: 68.5 (30-118) days post-HSCT [1] E= 1 (2.3%) C= 11 (22.9%) ($p=0.01$)	[1] Episodes of bacteraemia/100 days at risk in E= 0.19 (15.6%) versus C= 0.61 (58.3%) ($p=0.003$), episodes of Clostridium difficile diarrhea/100 days at risk in E= 0.13 versus C= 0.07 ($p=0.48$)	[1] Ciprofloxacin prophylaxis appears safe and effective in reducing the incidence of severe BKV-HC after allogeneic HSCT, with potential concomitant reduction in the risk of bacteremias
Vose et al. (1993) USA	Design: RCT Monocentric Duration: June, 1989 –May, 1991	E= 103 A Age: 34 years Gender M= 60 (58.2%) C= 97 A Age: 36 years Gender M= 54 (55.6%)	Low-dose CY= 100 (50%) High-dose CY= 100 (50%)	Intravenous mesna: 100% of CY dose started 1 h before the 1st CY dose, by continuous infusion, and continued for 24 h after last CY dose Intravenous hydration: normal saline at 250 mL/h	CBI: at 200 ml/h for 12 h after last CY dose at a minimum or until microhaematuria ended Intravenous hydration: normal saline at 250 mL/h	HC grading: I–IV (no specified classification) Time of appearance: ≤ 75 days post-HSCT E= 55 (53%) C= 74 (76%) ($p=0.007$) UTIs: E= 15 (14%) C= 26 (27%) ($p=0.03$)	Lower restriction of movement, bladder spasms, moderate to severe discomfort in E= 3 (2%) versus C= 82 (84%) ($p<0.0001$)	Both CBI and mesna were equally effective at preventing severe HC associated with high-dose CY. However, the use of mesna was associated with significantly less discomfort and a lower incidence of UTIs
Treatment Interventions								
Ippoliti et al. (1995) USA	Design: Phase I/II study Monocentric Duration:	E= 11 C= 13 A Age: 38 (21–48)	THIO/BU/CY= 20 (83.3%) THIO/CY/TBI= 3 (12.5%)	Clot evacuation by hand irrigation prior to intravesicular carboprost on day 32 (5–143) post-HSCT: 0.2	Intravesical carboprost: 0.8 mg/dl and escalated to 1.0 mg/dl after 4 doses continuing for 48 hours after resolution of	HC grading: III–IV (NCI CTCAE) Time of appearance: 18 (0–126) days post-	Bladder spasms in all patients. Symptomatic measures minimized the discomfort sufficiently to continue therapy	Intravesicular carboprost may provide a safe and inexpensive alternative for the treatment of refractory

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Table 1 (*continued*)

Methods						Findings		
Author, Country	Design, and duration	Population	Specific risk factors	Experimental (n)	Comparison (n)	Measures	Collateral effects	Linking evidence to practice
	March, 1993 – July, 1994	years Gender M = 12 (50%)	Carmustine/Etoposide/ Cytarabine/CY = 1 (4.1%)	mg/dl in 50 ml normal saline for 1 h every 6 hours and then clamped for 1 hour. Patients were instructed to change positions every 15 min. If not complete response after 4 doses, escalation by 0.2 mg/dl every 24 h until a maximum of 1.0 mg/dl or if a complete response is observed. Treatment was continued for 48 h after complete response for maximum of 14 days Salvage therapy after carboprost failure: platelet transfusions (=1), CBI (=1), cystoscopy and fulguration (=2), formalin instillation (=2), alum instillation and aminocaproic acid (=2) Supportive measures: oxybutynin orally 5–10 mg, belladonna, opium suppositories (=24)	haematuria for maximum 7 days. Changing positions every 15 min	HSCT Resolution with carboprost: 15 (63%) patients CR in 3 (1–12) days 9 (60.0%) patients reported a HC recurrence 8 (33.3%) patients had a resolution with salvage therapy		HC that should be considered prior to other invasive procedures
Lynch and Kajon (2016) USA	Design: review [1] La Rosa et al. (2001), monocentric retrospective USA	E = 1 C = 9 Age: - Gender: -	ADV viruria (90%)	Intravenous ribavirin for three-week course of therapy (9 days)	Intravenous ribavirin: -	HC grading: - Time of appearance: 26 (10-49) days post-HSCT Clinical improvement with intravenous ribavirin: none Clinical improvement without intravenous ribavirin: 5 (55.5%) patients	Not reported	The use of ribavirin therapy was not associated with an appreciable benefit
Mackey (2012)§ USA	Design: Literature review Duration: (-) [1] Ganguly et al. (2010), monocentric retrospective USA [2] Kawakami et al. (1997), monocentric prospective Japan	[1] E = 18 C = - A Age: 47 (22–68) years Gender M = 11 (61.1%) [2] E = 2 C = - A Age: 35.5 (25–46) years Gender M = 1 (50%)	[1] BK viruria = 18 (100%) [2] Ranimustina-splenic irradiation-CY-TBI = 2 (100.0%) ADV viruria = 2 (100.0%)	[1] Intravenous CDV: 0.5 mg/kg/dose once a week until symptom resolution (=14) [1] Intravenous CDV: 1 mg/kg/dose once a week after 2 weeks because of lack of response (=3) [1] Intravenous (0.5 mg/kg/dose) and intravesicular CDV: at 5 mg/kg/dose in 60 ml of normal saline through a Foley catheter in 15 min, clamped for 1 h (=4) [2] Intravenous vidarabine: 10 mg/kg per day for 5 days [2] Supportive measures: forced	-	HC grading: [1] - [2] 138 (26-250) days post-HSCT Time of appearance: [1] - [2] 43 (15–272) days post-HSCT Symptom resolution with CDV: [1] after 6 weeks of therapy in 13 (72%) patients [2] after 16 (11-30) days of therapy	[1] Worsening renal function = 3 (16.6%), local discomfort due to catheter insertion [2] Not reported	[1] First-line treatment with intravesicular CDV is recommended for symptomatic patients with isolated BK-viruria; for patients who fail to respond to intravesical route alone, it is suggested to add intravenous CDV. [2] Vidarabine was effective in one case of ADV-HC and not in the other

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Table 1 (*continued*)

Methods						Findings		
Author, Country	Design, and duration	Population	Specific risk factors	Experimental (n)	Comparison (n)	Measures	Collateral effects	Linking evidence to practice
				alkaline diuresis, oral hydration, analgesics and antibiotics as necessary, CBI with prostaglandin E1 bladder instillation if macroscopic hematuria, morphine for severe pain				
Philippe et al. (2016) France	Design: retrospective Monocentric Duration: March, 2011 – June, 2013	E= 27 C= - A Age: 42 (21–60) years Gender M= 15 (55.5%)	GVHD= 11 (40.7%) BK viruria= 26 (96.3%) ADV reactivation in blood= 1 (3.7%)	Intravenous CDV: median 5 mg/kg/dose in 4 median injections mostly once a week for 2 weeks and then 2 injections at 2-week intervals (=24) Intravesical CDV: median 5 mg/kg/dose in 4 median injections mostly once a week for 2 weeks and then 2 injections at 2-week intervals (=1) Intravenous CDV and intravesical CDV: median 5 mg/kg/dose in 4 median injections mostly once a week for 2 weeks and then 2 injections at 2-week intervals (=2) Oral probenecid: 2 g 3 hours before CDV administration and 1 g 3 hours and 9 hours after CDV (=26) Supportive measures: intravenous hydration with normal saline, bladder irrigation, blood transfusions, symptom relief (=27)	-	HC grading: I–IV (Bedi et al., 1995) Time of appearance: 63 (14–189) days post-HSCT Clinical response with CDV: 22 (81.5%) patients CR 2 (7.4%) patients PR 3 (11.1%) responders had a recurrence of HC (1 patient had a CR with intravesical CDV)	Renal failure: moderate= 6 (22.2%) and severe= 2 (7.4%)	The study showed that intravenous CDV is an effective treatment for BKV-HC in allo-HSCT patients but requires renal toxicity management. Given the retrospective study design and the probable multifactorial origin of renal failure, results should be interpreted with caution
Philippe et al. (2016) France	Design: Literature review Duration: last search 2015 [1] Savona et al. (2007), retrospective monocentric USA [2] Gilis et al. (2014), retrospective monocentric France [3] Lee et al. (2015),	E= [1] 19 [2] 39 [3] 8 C= [1] (-) [2] 4 [3] (-) A Age: [1] 42 (20–64) years [2] 40 (24–64) years [3] 33 (19–50) years Gender M: [1]= 12 (63.1%) [2]= 25	[1] BK viruria= 19 (100%) GVHD= 16 (84%) CMV viruria= 1 (5.2%) [2] BK viruria= 39 (100%) TBI= 25 (58.1%) BU= 15 (34.9%) ATG= 32 (74.4%) GVHD= 6 (14%) [3] GVHD= 7 (87.5%) FLU/BU/ATG= 6 (75%) TBI/CY/ATG= 1 (12.5%) TBI/CY/etoposide= 1 (12.5%)	[1] Intravenous CDV: 1 mg/kg weekly dose in 4.5 median injections [2] Intravenous CDV: 5 mg/kg average dose in 4 delivered injections for a median duration of 26 days. Salvage therapy after CDV failure: hyperbaric oxygen therapy (=7), alum instillation (=5), cauterization or embolization (=7) and cystectomy (=1) [3] Intravenous CDV: 1 mg/kg/dose in 100 mL of normal saline weekly for a median of 4 doses	[2] CDV: - (=4) Oral ciprofloxacin (=1) Polyvalent immunoglobulin infusions (=1)	HC grading: [1] I–III (Bedi et al., 1995) [2] I–IV (Bedi et al., 1995) [3] II–III (classification not specified) Time of appearance: [1] 68.7 (18–215) days post-HSCT [2] 37 (9–361) days post-HSCT [3] 69 (16–311) days post-HSCT Clinical response with CDV: [1] 16 (84%) of patients	[1] Renal toxicity= 5 (26.3%) [2] Renal toxicity= 33 (84.6%) (p=0.98) [3]Renal toxicity= 3 (37.5%), thrombocytopenia= 1 (12.5%)	Intravenous CDV is a valid treatment for BKV-HC but requires close renal surveillance. There are very few other alternatives, but no efficacy-based new treatment appears to substitute cidofovir for curative use. To limit kidney damage, the intravesical route should be tried

(*continued on next page*)

Table 1 (*continued*)

Methods					Findings		
Author, Country	Design, and duration	Population	Specific risk factors	Experimental (n)	Comparison (n)	Measures	Collateral effects	Linking evidence to practice
	retrospective monocentric Korea	(58.1%) [3] = 5 (62.5%)		Hyperhydration CBI 400 mg/day Fluoroquinolones Intravesical hyaluronic acid: at 40 mg in 50 mL of normal saline for 20 minutes each week		[2] 25 (64%) patients CR. 3 (8%) patients PR. 13 (33.3%) patients had a clinical improvement with salvage therapy [3] 7 (87.5%) of patients		

Abbreviations:
§Mackey (2012) was emerged also in Satyanarayana et al. (2014)
[166]Ho-DOTMP: [166]holmium-1,4,7,10-tetraazacyclododecane-1,4,7,1-tetramethylene phosphonate; A: Average; ADV: Adenovirus; ATG: Antithymocyte Globulin; BU: Busulfan; BKV: BK Virus; C: Comparison; CBI: Continuous Bladder Irrigation; CDV: Cidofovir; CI: Confidence Interval; CMV: Cytomegalovirus; CR: Complete Response; CY: Cyclophosphamide; E: Exposed; FLU: Fludarabine; GVHD: Graft Versus Host Disease; HC: Haemorrhagic Cystitis; HSCT: Haematopoietic Stem Cell Transplantation; M: Male; MEL: Melphalan; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PR: Partial Response; SD: Standard Deviation; TBI: Total Body Irradiation; THIO: Thiotepa; UTIs: Urinary Tract Infections.

studies (Miller et al., 2011).

The review of Mackey (2012) included studies performed from 1997 to 2010 and Philippe et al. (2016) from 2005 to 2015. Primary studies collected data from 1989 (Vose et al., 1993) to 2015 (Philippe et al., 2016). However, Breitz et al. (2003) did not report when data collection was performed; Lynch and Kajon (2016) and Satyanarayana et al. (2014) did not report the timeframe used in the process of study inclusion.

Studies retrieved included from two (Kawakami et al., 1997) to 200 patients (Vose et al., 1993). Six studies showed a male gender predominance (Bedi et al., 1995; Ganguly et al., 2010; Gonella et al., 2015; Hadjibabaie et al., 2008; Mackey, 2012; Vose et al., 1993). The included patients were affected by different clinical conditions (for example, acute myeloid/lymphoblastic leukaemia, chronic myeloid leukaemia); Vose et al. (1993) also included patients with non-haematological diseases such as breast cancer, sarcoma, neuroblastoma, thymoma, and uterine cervix cancer.

Some patients had undergone autologous transplantation (Breitz et al., 2003; Giralt et al., 2003), allogeneic transplantation from siblings (Hadjibabaie et al., 2008; Kawakami et al., 1997; Lee et al., 2015; Miller et al., 2011; Mackey, 2012; Philippe et al., 2016; Savona et al., 2007), auto and allogeneic transplantation (Bedi et al., 1995; Gonella et al., 2015; Ippoliti et al., 1995; La Rosa et al., 2001; Vose et al., 1993), Matched Unrelated Donor transplantation (Ganguly et al., 2010; Gonella et al., 2015; Kawakami et al., 1997; Miller et al., 2011; Mackey, 2012; Savona et al., 2007) and allogeneic transplantation from the umbilical cord (Ganguly et al., 2010; Gilis et al., 2014; Gonella et al., 2015; Lee et al., 2015; Miller et al., 2011; Philippe et al., 2016).

Seven primary studies were focused on the effectiveness of preventive interventions (Bedi et al., 1995; Breitz et al., 2003; Giralt et al., 2003; Gonella et al., 2015; Hadjibabaie et al., 2008; Miller et al., 2011; Vose et al., 1993) and eight on treatments (Ippoliti et al., 1995; Ganguly et al., 2010; La Rosa et al., 2001; Kawakami et al., 1997; Savona et al., 2007; Gillis et al., 2014; Lee et al., 2015; Philippe et al., 2016) among HSCT adult population.

3.2. Preventive interventions

As reported in Table 1, the first preventive intervention regarding HC among adult HSCT patients, dated back to 1993 when Vose et al. (1993) randomized 200 patients to receive intravenous mesna (daily dose of 100% of the daily cyclophosphamide [CY] dose), from 1 h before the first CY administration by continuous infusion, and at 24 h after the last CY dose (=103). In the other study arm (=97), patients received CBI with normal saline at 200 mL/h through a three-way Foley catheter for 12 h after the end of CY administration. Furthermore, all patients received intravenous hydration with normal saline at a rate of 250 mL/h.

A few years later, the mesna was administered at 60 mg/kg per day (120% of the daily CY dose) in five intravenous doses 30 min before and 3, 6, 9, and 12 h after each dose of CY (n = 71) (Bedi et al., 1995). All patients received intravenous hydration and furosemide if the urine output decreased <1.5 mL/kg/h in any 4-h period, the urine specific gravity was >1.010, or if the body weight increased >1 kg with respect to that recorded on admission.

Ten years later, Breitz et al. (2003) and Giralt et al. (2003) studied the effectiveness of CBI (at 200 mL/h) compared to hydration and frequent voiding every 2 h: they studied the same population (n = 83), who received escalation doses of radiotherapy with 20–40 Gy of [166]Ho-DOTMP in addition to melphalan (140–200 mg/m^2) and Total Body Irradiation (TBI) (8 Gy).

The two most recent preventive studies focused on patients receiving CBI (Gonella et al., 2015; Hadjibabaie et al., 2008). The treated group in the non-randomized controlled trial by Hadjibabaie et al. (2008) was subjected to CBI with normal saline at a rate of 300 mL/h, starting 12 h before the first dose of CY in addition to intravenous

Table 2
Trends in effectiveness of preventive and treatment interventions for HC.

Preventive Interventions	Studies	Microscopic haematuria	Macroscopic haematuria	Bladder toxicity using dosimetry MIRD
CBI	Vose et al. (1993)		↓	
	Breitz et al. (2003)			↑
	Giralt et al. (2003)			↑
	Hadjibabaie et al. (2008)		↑	
	Gonella et al. (2015)	↓		
Mesna	Vose et al. (1993)		↑	
	Bedi et al. (1995)		↑	
	Hadjibabaie et al. (2008)		↑	
	Gonella et al. (2015)	↑		
Intravenous hydration	Hadjibabaie et al. (2008)		↑	
	Gonella et al. (2015)	↑		
Hyperhydration and forced diuresis	Bedi et al. (1995)		↑	
	Breitz et al. (2003)			↓
	Giralt et al. (2003)			↓
Diuresis alkalinization	Hadjibabaie et al. (2008)		↑	
	Gonella et al. (2015)	↑		
Fluoroquinolones	Gonella et al. (2015)	↕		
Orally ciprofloxacin	Miller et al. (2011)		↑	

Treatment Interventions	Studies	Resolution of macroscopic haematuria for 48 hours after end of treatment	Subjective or clinically improvement in symptoms or reduction of HC grade	Full symptom remission of HC
Intravesical carboprost	Ippoliti et al. (1995)	↑		
Intravenous CDV	Ganguly et al. (2010)			↑
	Gilis et al. (2014)			↑
	Lee et al. (2015)		↑	
	Philippe et al. (2016)			↑
	Savona et al. (2007)		↑	
Intravesical CDV	Philippe et al. (2016)			↑
Intravenous and intravesical CDV	Ganguly et al. (2010)			↑
	Philippe et al. (2016)			↕
Intravenous ribavirin	La Rosa et al. (2001)		↓	
Intravenous vidarabine	Kawakami et al. (1997)		↕	
Immunoglobulin infusions	Gilis et al. (2014)		↑	
Oral probenecid	Philippe et al. (2016)			↕
Intravesical hyaluronic acid	Lee et al. (2015)		↕	
Formalin and alum instillation	Gilis et al. (2014)		↑	
	Ippoliti et al. (1995)	↑		
Oral ciprofloxacin	Gilis et al. (2014)		↑	
Aminocaproic acid	Ippoliti et al. (1995)	↑		
Hyperbaric oxygen therapy	Gilis et al. (2014)		↑	
Position change after intravesical instillation	Ippoliti et al. (1995)	↕		
CBI	Ippoliti et al. (1995)	↑		
	Lee et al. (2015)		↕ (to reduce BKV viral load)	
	Philippe et al. (2016)*			↕
Fulguration/ cauterization	Gilis et al. (2014)		↑	
	Ippoliti et al. (1995)	↑		
Cystectomy	Gilis et al. (2014)		↑	

Abbreviations:
CBI: Continuous Bladder Irrigation; CDV: Cidofovir; HC: Haemorrhagic Cystitis; MIRD: Medical Internal Radiation Dosimetry.
↑: effective; ↓: ineffective ↕: no indicators of/data on effectiveness; *as supportive measure

mesna, vigorous hydration with dextrose water or normal saline containing potassium chloride, and alkalinization with sodium bicarbonate. The control group did not receive CBI. Gonella et al. (2015) instead studied the effectiveness of mesna: 51 patients were catheterized and underwent CBI at a rate of 300 mL/h of normal saline through a three-way Foley catheter on the day of the first dose of CY until 48/72 h after the last drug dose. The other 107 recipients did not undergo CBI. All patients received mesna (3863 mL daily) and hyperhydration (2500 mL daily) with the exception of one patient (n = 157) who was allergic to the medication; 147 patients received sodium bicarbonate (980 mL daily) for diuresis alkalinization while 139 received antibiotic prophylaxis with fluoroquinolones.

Regarding the preventive interventions tested, different dosages and timings were used across studies: for example, mesna was started from 30 (Bedi et al., 1995) to 60 min (Vose et al., 1993) before the first infusion of CY and was continued until 12 (Bedi et al., 1995), 18 (Hadjibabaie et al., 2008) or 24 h (Vose et al., 1993) after the last dose of CY. Mesna was administered through a bolus route with repeated administration (Bedi et al., 1995; Hadjibabaie et al., 2008) or by continuous infusion (Vose et al., 1993). Gonella et al. (2015) did not specify the administration route. Daily mesna dose was established in relation to the daily dose of CY, ranging from 100% to 120% of the daily CY dose (Bedi et al., 1995; Hadjibabaie et al., 2008; Vose et al., 1993).

Moreover, CBI with normal saline was administered at 200 mL/h (Giralt et al., 2003; Vose et al., 1993) and 300 mL/h (Gonella et al., 2015; Hadjibabaie et al., 2008) prior to and until the day following ^{166}Ho-DOTMP (Giralt et al., 2003), or until 12 (Vose et al., 1993) or 48 h (Gonella et al., 2015; Hadjibabaie et al., 2008) after the last CY dose. Breitz et al. (2003) did not specify the solution used, nor the speed of the CBI.

Intravenous hyperhydration was also performed in all preventive studies with different dosages and/or timings: Gonella et al. (2015) and Vose et al. (1993) used 250 mL/h, whereas Bedi et al. (1995) reported a

dosage of 2 mL/kg/h from 12 h before CY until 24 h after the last CY dose. Finally, Giralt et al. (2003) and Hadjibabaie et al. (2008) administered normal saline and 5% dextrose at the rate of 200 mL/h. Breitz et al. (2003) did not specify the solution infused.

Differently from the preventive strategies studied by above-mentioned authors, Miller et al. (2011), focused upon the preventive effectiveness of oral ciprofloxacin by administering 500 mg every 12 h from the day of transplantation until the 60th day after the transplantation.

3.3. Treatment interventions

As reported in Table 1, the first two treatment studies regarding HC among adult HSCT patients performed in the late 1990s aimed to establish the effectiveness of (a) intravesical carboprost, a prostaglandin $F_2\alpha$ analogue, and (b) intravenous vidarabine. With regards to the first study, Ippoliti et al. (1995) treated 24 adults with escalating doses of carboprost, after failure of first-line therapy. In Phase I, a total of 11 patients received carboprost at 0.2 mg/dL in 50 mL saline instilled into the bladder for 60 min every 6 h within 1 h of preparation. During this time, the bladder catheter was clamped, and patients were instructed to change position every 15 min. Prior to each administration of carboprost, clots were evacuated from the bladder by hand irrigation. In Phase II, carboprost was initiated in 13 patients at a dose of 0.8 mg/dL; among the eight patients who did not respond to carboprost initially, two were treated with cystoscopy and fulguration, one with formalin instillation, two with alum instillation and administration of aminocaproic acid, and one each with platelet transfusion or CBI.

With regards to the second, Kawakami et al. (1997), performed a case series study by including six patients and two of them developed HC. Intravenous vidarabine was administered at the dose of 10 mg/kg/day for five days.

In more recent years, Ganguly et al. (2010) investigated how to treat BKV-associated HC using the antiviral cidofovir (CDV). They administered intravenous CDV in 18 patients symptomatic to BK virus at 0.5 mL/kg once a week, and four patients required combination therapy using the intravesical route (5 mg/kg in 60 mL of normal saline within 15 min until symptom resolution); the bladder catheter was clamped for 60 min after infusion.

The effectiveness of CDV was also documented by Philippe et al. (2016) in their retrospective study in which intravenous CDV (5 mg/kg median dose in four median injections mostly once a week for 2 weeks and then two injections at 2-week intervals) was administered in 24 patients; the intravesical route and the intravenous plus intravesical one was used in one and two patients, respectively. Oral probenecid was given 3 h before CDV and 3 h after the end of CDV to reduce bladder toxicity. Finally, Lee et al. (2015) and Savona et al. (2007) administered low-dose CDV (1 mg/kg) for a median of four doses while Gilis et al. (2014) administered high-dose CDV (5 mg/kg average dose) in four injections, once a week for a median duration of 26 days.

In patients who manifested clinical failure after CDV or carboprost administration, a salvage therapy contributed to the resolution of HC: alum instillation and cauterization/fulguration were applied in both Ippoliti et al. (1995) and Gilis et al. (2014).

3.4. Studied outcomes and trends

As reported in Table 2, the effectiveness of the preventive interventions was measured by considering the reduction in appearance of micro- and macroscopic haematuria (Bedi et al., 1995; Breitz et al., 2003; Giralt et al., 2003; Gonella et al., 2015; Miller et al., 2011; Hadjibabaie et al., 2008; Vose et al., 1993) using different methods of grading. In Breitz et al. (2003) and Giralt et al. (2003) the appearance of haematuria was scored using the NCI score (NCI, 2018); Hadjibabaie et al. (2008) used the Droller et al. (1982) score while Gonella et al. (2015) used a more recent score developed by Leung et al. (2002). Moreover, Bedi et al. (1995) used a score developed by themselves (Bedi et al., 1995) while Vose et al. (1993) did not report the score used.

Methods used to measure the outcomes varied: for example, midstream urine specimens were collected and examined before cytotoxic therapy, twice a week during hospital stay and during each weekly clinic visit after patient discharge (Bedi et al., 1995). Bladder toxicity related to radiotherapy was determined using dosimetry (MIRD dynamic bladder model) (Breitz et al., 2003; Giralt et al., 2003) and by collecting and analysing urine samples at 0–6-h intervals (Giralt et al., 2003).

However, according to the findings, they showed positive trends of effectiveness with regard to mesna, intravenous hydration and diuresis alkalinisation and for the ciprofloxacin; in contrast, there is a non-homogeneous trend for the effectiveness of CBI across studies, as reported in Table 2.

The effectiveness of treatment interventions has also been investigated by considering the complete response to the intervention applied, as defined by (a) the resolution of macroscopic haematuria for 48 h after the end of treatment (Ippoliti et al., 1995), (b) the subjective or clinical improvement in symptoms or reduction in grade of HC severity (La Rosa et al., 2001; Lee et al., 2015; Kawakami et al., 1997; Savona et al., 2007) or (c) in the full symptom remission of HC (Ganguly et al., 2010; Gilis et al., 2014; Philippe et al., 2016). Moreover, partial responses such as the downgrading of BKV-HC severity have also been reported (Gilis et al., 2014; Philippe et al., 2016).

According to the findings, there are positive trends of effectiveness with regard to CDV, carboprost, formalin and alum instillations, as reported in Table 2.

3.4.1. Secondary research outcomes

Secondary outcomes were pain (Ippoliti et al., 1995; Vose et al., 1993) and discomfort (Ganguly et al., 2010; Gonella et al., 2015; Hadjibabaie et al., 2008; Vose et al., 1993) but no specific tools were used to detect their intensity. Moreover, discomfort was reported as mild (Gonella et al., 2015; Hadjibabaie et al., 2008) or moderate–severe (Vose et al., 1993) and was associated with bladder spasms (Ippoliti et al., 1995; Vose et al., 1993), restriction in movements (Vose et al., 1993) or the insertion of a Foley catheter and CBI (Ganguly et al., 2010; Ippoliti et al., 1995; Vose et al., 1993).

4. Discussion

4.1. Study methodological features

Studies relating to the topic under consideration are sparse and require further investments with larger, multicentre, and longitudinal study designs conducted at the international level. In fact, only 15 primary studies were identified regarding patients undergoing HSCT: most of them were performed in the USA, and were mainly based upon retrospective and monocentric study designs. These studies were published from 1993 (Vose et al., 1993) to 2016 (Philippe et al., 2016), a period in which the number of transplants increased (EBMT, 2018). However, despite the documented prevalence and incidence of HC (Hadjibabaie et al., 2008; Tsuboi et al., 2003), as well as its negative impact on patients (Cesaro et al., 2013), studies have only included small sample sizes to date.

Gender was not always equally represented across studies, with a tendency to include male patients in six primary out of 15; the age of the included patients was wide, ranging from 19 (Lee et al., 2015) to 71 years (Giralt et al., 2003), possibly because age is not considered as a risk factor in developing HC (Gonella et al., 2015; Xu et al., 2007). However, studies included patients undergoing different transplantation strategies (for example, autologous, allogeneic) that have been documented as having different risks of HC with a higher incidence among allogeneic transplantation (Gonella et al., 2015; Vose et al., 1993; Xu et al., 2007).

4.1.1. Preventive interventions

Preventive studies have analyzed the role of intravenous mesna

(Bedi et al., 1995) and that of mesna as compared to CBI (Vose et al., 1993). In more recent years, authors have compared CBI to hyperhydration (Breitz et al., 2003; Giralt et al., 2003; Gonella et al., 2015; Hadjibabaie et al., 2008). However, the most studied intervention to date has been the administration of CBI, as reported in five studies (Breitz et al., 2003; Giralt et al., 2003; Gonella et al., 2015; Hadjibabaie et al., 2008; Vose et al., 1993) and the intravenous administration of mesna, as reported in four studies (Bedi et al., 1995; Gonella et al., 2015; Hadjibabaie et al., 2008; Vose et al., 1993). Moreover, preventive measures have often been studied in combination, as in Bedi et al. (1995), where the effectiveness of mesna was investigated in addition to two interventions (hydration and furosemide) against forced diuresis only; and in Breitz et al. (2003) and Giralt et al. (2003), where CBI was compared to hyperhydration and forced diuresis. Furthermore, four interventions (mesna, intravenous hydration, diuresis alkalinization and administration of fluoroquinolones) were investigated in combination by Gonella et al. (2015) and Hadjibabaie et al. (2008).

With regard to studies investigating the same interventions, a wide variety of dosages, timings, and routes of administration have been used: in retrospective study designs, this can be due to the different practices and protocols already used in the involved units. However, future studies should be based on standardized methods of preventive intervention administration and a standardized set of data should be reported.

4.1.2. Treatment interventions

CDV has been the most investigated HC treatment, with intravenous administration in five studies (Ganguly et al., 2010; Gilis et al., 2014; Lee et al., 2015; Philippe et al., 2016; Savona et al., 2007), intravesical administration in one study (Philippe et al., 2016), and both intravenous and intravesical administration in two studies (Ganguly et al., 2010; Philippe et al., 2016). In contrast, intravesical carboprost was only documented by Ippoliti et al. (1995), in whose study patients were also asked to frequently change their position after the instillation, without reporting data concerning their perceptions.

Concerning CVD administration, there has been great variability across studies, for example, in the retrospective section of Philippe et al.'s study (2016), authors reported the use of intravenous CDV in addition to intravesical administration in one patient; the same combination was reported in four patients by Ganguly et al. (2010). Moreover, in the retrospective section of Philippe et al.'s (2016) study, intravenous CDV was given in association with oral probenecid aimed at reducing the risk of renal failure; in contrast, one primary study administered intravenous CDV in combination with four other measures: hyperhydration, CBI, fluoroquinolones and hyaluronic acid (Lee et al., 2015). Furthermore, in addition to the different routes of administration or combinations of interventions, administration procedures also varied: for example, the dosage of intravenous CDV ranged from a minimum of 0.5 mg/kg/dose once a week (Ganguly et al., 2010) to a maximum of 5 mg/kg/dose weekly (Philippe et al., 2016). The median number of CDV injections was reported in four injections in Philippe et al. (2016) and in six in Ganguly et al. (2010), where administration was continued until the resolution of symptoms. Only Lee et al. (2015) administered CDV diluted in normal saline solution. In addition, only two studies provided a salvage therapy (Ippoliti et al., 1995; Gilis et al., 2014), suggesting that future studies testing HC treatments should be based on standardized methods of intervention administration as well as on a standardized data reporting system aimed at supporting both clinicians and researchers in their decision-making.

4.2. Primary and secondary study outcomes and trends

The administration of mesna, intravenous hydration and diuresis alkalinization seem to be effective at preventing HC, while intravenous CDV appears to be the most effective treatment. Contrarily, CBI showed variable preventive effectiveness among studies (Gonella et al., 2015; Hadjibabaie et al., 2008).

As primary outcomes, macroscopic and microscopic haematuria were considered as indicators of effectiveness among the preventive studies. In contrast, full symptom remission of HC, resolution of macroscopic haematuria for 48 h after treatment and subjective improvement in symptoms or reduction of HC grade were reported as indicators of effectiveness in treatment studies. Moreover, even the severity of HC was measured using different tools: for example, the NCI CTCAE score was used in three studies (Breitz et al., 2003; Giralt et al., 2003; Ippoliti et al., 1995), and the Leung et al. (2002) and Droller et al. (1982) scores in two (Gonella et al., 2015; Hadjibabaie et al., 2008). Therefore, it is recommended that future studies use standardized measures of outcomes aimed at increasing the ability to compare findings and to perform a meta-analysis.

Pain and discomfort were the most frequent symptoms reported; Gonella et al. (2015) suggested to consider the risk/benefit ratio of preventive catheterization and CBI as associated with discomfort and a high risk of UTIs. Moreover, only Vose et al. (1993) reported side effects perceived by patients as physical discomfort associated with CBI and bladder catheterization on a daily basis. Other studies documented effects as reported by clinicians, suggesting that future studies should also consider the patients' perspective by using valid instruments to record their perceptions.

4.3. Limitations

This scoping review has several limitations: although based upon a systematic approach, where also handsearching was performed, some studies could have been missed. Moreover, only studies as emerged in three databases and published in English were included, therefore introducing a potential selection bias.

Researchers classified the emerged interventions as preventive or treatment according to their main intent. However, some studies reported also some supportive measures (for example, Philippe et al., 2016) while other did not (for example, Gilis et al., 2014). Authors are encouraged to report the intent of each intervention under study thus allowing for comparison of their effectiveness.

5. Conclusions

The intent of the stud was to map HC prevention and treatment interventions in adult hematological patients after transplantation as researched to date aiming at identifying more focused lines of research. Studies emerged are sparse, monocentric in nature, and with high heterogeneity in methods, interventions, and measures thus preventing the establishment of gold standards in a clinical field where, due to HC, the quality of life is further decreased in addition to that compromised by the underlying disease and treatments.

To date, the studied preventive interventions have been intravenous hyperhydration, alkalinization of urine, forced diuresis, administration of mesna, and CBI, with conflicting findings. HC treatment studies have been more often documented, and mainly reported the intravesical and intravenous administration of cidofovir with positive trends in effectiveness.

Nurses can have a great role in designing further studies aiming at establishing preventive strategies. Moreover, also those focused upon treatment interventions, all require methodologically sound studies using homogeneous outcomes, with more standardized approaches in intervention administration procedures. There is also a need to design longitudinal and multicentric studies thus capable of involving large groups of patients, whose perceptions and experience should also be taken into account.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejon.2019.07.005.

References

Bedi, A., Miller, C.B., Hanson, J.L., Goodman, S., Ambinder, R.F., Charache, P., Arthur, R.R., Jones, R.J., 1995. Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. J. Clin. Oncol. 13, 1103–1109. https://doi.org/10.1200/JCO.1995.13.5.1103.

Breitz, H., Wendt, R., Stabin, M., Bouchet, L., Wessels, B., 2003. Dosimetry of high dose skeletal targeted radiotherapy (STR) with 166Ho-DOTMP. Cancer Biother. Radiopharm. 18 (2), 225–230. https://doi.org/10.1089/108497803765036391.

Bridges, B., Donegan, S., Badros, A., 2006. Cidofovir bladder instillation for the treatment of BK virus hemorrhagic cystitis after allogeneic stem cell transplantation. Am. J. Hematol. 81, 535–537. https://doi.org/10.1002/ajh.20567.

Cesaro, S., Pillon, M., Tridello, G., Aljurf, M., Martino, R., Schroyens, W., Nozzoli, C., Barba, P., Faraci, M., Fagioli, F., Cappelli, B., Cordonnier, C., Al-Mohareb, F., Floisand, Y., Greil, J., Panizzolo, I.S., Santarone, S., 2013. Relationship between clinical and BK virological response in patients with late hemorrhagic cystitis treated with cidofovir: a retrospective study from the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 48, 809–813. https://doi:10.1038/bmt.2012.247.

Droller, M.J., Saral, R., Santos, G., 1982. Prevention of cyclophosphamide- induced hemorrhagic cystitis. Urology 20, 256–258. https://doi.org/10.1016/0090-4295(82)90633-1.

Dropulic, L.K., Jones, R.J., 2008. Polyomavirus BK infection in blood and marrow transplant recipients. Bone Marrow Transplant. 41, 11–18. https://doi:10.1038/sj.bmt.1705886.

European Society for Blood and Marrow Transplantation (EBMT), 2018. Annual Report/18. . https://www.ebmt.org/sites/default/files/2019-03/EBMT%20Annual%20Report%202018.pdf.

Eisen, D.P., Fraser, I.R., Sung, L.M., Finlay, M., Bowden, S., O'Connell, H., 2009. Decreased viral load and symptoms of polyomavirus-associated chronic interstitial cystitis after intravesical cidofovir treatment. Clin. Infect. Dis. 48, 86–88. https://doi.org/10.1086/597827.

Federoff, A., 2008. BK virus in hematopoietic stem cell transplantation recipients. Clin. J. Oncol. Nurs. 12, 895–900. https://doi:10.1188/08.

Focosi, D., Maggi, F., Pistolesi, D., Benedetti, E., Papineschi, F., Galimberti, S., Ceccherini-Nelli, L., Petrini, M., 2009. Hyperbaric oxygen therapy in BKV-associated hemorrhagic cystitis refractory to intravenous and intravesicular cidofovir: case report and review of literature. Leuk. Res. 33, 556–560. https://doi:10.1016.2008.06.018.

Ganguly, N., Clough, L.A., DuBois, L.K., Mcguirk, J.P., Abhyankar, S., Alijitawi, O.S., O'Neal, N., Divine, C.L., Ganguly, S., 2010. Low-dose cidofovir in the treatment of symptomatic BK virus infection in patients undergoing allogeneic hematopoietic stem cell transplantation: a retrospective analysis of an algorithmic approach. Transpl. Infect. Dis. 12, 406–411. https://doi: 10.1111/j.1399-3062.2010.00513.x.

Gaziev, J., Paba, P., Miano, R., Germani, S., Sodani, P., Bove, P., Perno, C.F., Marziali, M., Gallucci, C., Isgrò, A., Paciaroni, K., Roveda, A., Simone, M.D., De Angelis, G., Alfieri, C., Lucarelli, G., 2010. Late-onset hemorrhagic cystitis in children after hematopoietic stem cell transplantation for thalassemia and sickle cell anemia: a prospective evaluation of polyoma (BK) virus infection and treatment with cidofovir. Biol. Blood Marrow Transplant. 16, 662–671. https://doi.org/10.1016/j.bbmt.2009.12.009.

Gilis, L., Morisset, S., Billaud, G., Ducastelle-Leprêtre, S., Labussière-Wallet, H., Nicolini, F.E., Barraco, F., Detrait, M., Thomas, X., Tedone, N., Sobh, M., Chidiac, C., Ferry, T., Salles, G., Michallet, M., Ader, F., Lyon BK virus Study group, 2014. High burden of BK virus-associated hemorrhagic cystitis in patients undergoing allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 49, 664–670. https://doi:10.1038/bmt.2013.235.

Giralt, S., Bensinger, W., Goodman, M., Podoloff, D., Eary, J., Wendt, R., Alexanian, R., Weber, D., Maloney, D., Holmberg, L., Rajandran, J., Breitz, H., Ghalie, R., Champlin, R., 2003. 166Ho-DOTMP plus melphalan followed by peripheral blood stem cell transplantation in patients with multiple myeloma: results of two phase 1/2 trials. Blood 102, 2684–2691. https://doi.org/10.1182/blood-2002-10-3250.

Gonella, S., Di Pasquale, T., Palese, A., 2015. Preventive measures for cyclophosphamide-related hemorrhagic cystitis in blood and bone marrow transplantation: an Italian multicenter retrospective study. Clin. J. Oncol. Nurs. 19, E8–E14. https://doi.org/10.1188/15.CJON.E8-E14.

Hadjibabaie, M., Alimoghaddam, K., Shamshiri, A.R., Iravani, M., Bahar, B., Mousavi, A., Jahani, M., Khodabandeh, A., Anvari, Y., Gholami, K., Ghavamzadeh, A., 2008. Continuous bladder irrigation prevents hemorrhagic cystitis after allogeneic hematopoietic cell transplantation. Urol. Oncol. 26, 43–46. https://doi.org/10.1016/j.urolonc.2006.12.015.

Ippoliti, C., Przepiorka, D., Mehra, R., Neumann, J., Wood, J., Claxton, D., Gajewski, J., Khouri, I., van Besien, K., Andersson, B., Deisseroth, A.B., Dinney, C.P., 1995. Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. Urology 46, 811–815. https://doi.org/10.1016/S0090-4295(99)80349-5.

Kawakami, M., Ueda, S., Maeda, T., Karasuno, T., Teshima, H., Hiraoka, A., Nakamura, H., Tanaka, K., Masaoka, T., 1997. Vidarabine therapy for virus-associated cystitis after allogeneic bone marrow transplantation. Bone Marrow Transplant. 20, 485–490.

La Rosa, A.M., Champlin, R.E., Mirza, N., Gajewski, J., Giralt, S., Rolston, K.V., Raad, I., Jacobson, K., Kontoyiannis, D., Elting, L., Whimbey, E., 2001. Adenovirus infections in adult recipients of blood and marrow transplants. Clin. Infect. Dis. 32 (6), 871–876.

Laszlo, D., Bosi, A., Guidi, S., Saccardi, R., Vannucchi, A.M., Lombardini, L., Longo, G., Fanci, R., Azzi, A., De Santis, R., Rossi Ferrini, P., 1995. Prostaglandin E2 bladder instillation for the treatment of hemorrhagic cystitis after allogeneic bone marrow transplantation. Haematologica 80, 421–425.

Lee, G.W., Lee, J.H., Choi, S.J., Kim, S., Seol, M., Kim, W.K., Lee, J.S., Lee, K.H., 2003. Hemorrhagic cystitis following allogeneic hematopoietic cell transplantation. J. Korean Med. Sci. 18, 191–195. https://doi.org/10.3346/jkms.2003.18.2.191.

Lee, S.S., Ahn, J.S., Jung, S.H., Ahn, S.Y., Kim, J.Y., Jang, H.C., Kang, S.J., Jang, M.O., Yang, D.H., Kim, Y.K., Lee, J.J., Kim, H.J., 2015. Treatment of BK virus-associated hemorrhagic cystitis with low-dose intravenous cidofovir in patients undergoing allogeneic hematopoietic cell transplantation. Korean J. Intern. Med. 30, 212–219. https://doi.org/10.3904/kjim.2015.30.2.212.

Leung, A.Y., Mak, R., Lie, A.K., Yuen, K.Y., Cheng, V.C., Liang, R., Kwong, Y.L., 2002. Clinicopathological features and risk factors of clinically overt haemorrhagic cystitis complicating bone marrow transplantation. Bone Marrow Transplant. 29, 509–513. https://doi.org/10.1038/sj.bmt.1703415.

Levac, D., Colquhoun, H., O'Brien, K.K., 2010. Scoping studies: advancing the methodology. Implement. Sci. 5:69. https://doi.org/10.1186/1748-5908-5-69.

Lynch, J.P., Kajon, A.E., 2016. Adenovirus: epidemiology, global spread of novel serotypes, and advances in treatment and prevention. Semin. Respir. Crit. Care Med. 37, 586–602.

Mackey, M.C., 2012. Intravesicular cidofovir for the treatment of polyomavirus-associated hemorrhagic cystitis. Ann. Pharmacother. 46, 442–446. https://doi.org/10.1345/aph.1Q430.

Mani, J., Jin, N., Schmitt, M., 2014. Cellular immunotherapy for patients with reactivation of JC and BK polyomaviruses after transplantation. Cytotherapy 16 (10), 1325–1335. https://doi.org/10.1016/j.jcyt.2014.04.003.

Miller, A.N., Glode, A., Hogan, K.R., Schaub, C., Kramer, C., Stuart, R.K., Costa, L.J., 2011. Efficacy and safety of ciprofloxacin for prophylaxis of polyomavirus BK virus-associated hemorrhagic cystitis in allogeneic hematopoietic stem cell transplantation recipients. Biol. Blood Marrow Transplant. 17 (8), 1176–1181. https://doi.org/10.1016/j.bbmt.2010.12.700.

Miodosky, M., Abdul-Hai, A., Tsirigotis, P., Or, R., Bitan, M., Resnick, I.B., Gesundheit, B., Zilberman, I., Ioffe, L., Leubovic, A., Slavin, S., Shapira, M.Y., 2006. Treatment of post-hematopoietic stem cell transplantation hemorrhagic cystitis with intravesicular sodium hyaluronate. Bone Marrow Transplant. 38, 507–511. https://doi.org/10.1038/sj.bmt.1705474.

Miyamura, K., Hamaguchi, M., Taji, H., Kanie, T., Kohno, A., Tanimoto, M., Saito, H., Kojima, S., Matsuyama, T., Kitaori, K., Nagafuji, K., Sato, T., Kodera, Y., 2000. Successful ribavirin therapy for severe adenovirus hemorrhagic cystitis after allogeneic marrow transplant from close HLA donors rather than distant donors. Bone Marrow Transplant. 25, 545–548. https://doi.org/10.1038/sj.bmt.1702195.

Moher, D., Liberati, A., Tetzlaff, J., Altma, D.G., for the PRISMA Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Br Med J 339:b2535. https://doi.org/10.1136/bmj.b2535.

National Cancer Institute (NCI), 2018. Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50, Accessed date: 8 April 2019.

Paduch, D.A., 2007. Viral lower urinary tract infections. Curr. Urol. Rep. 8, 324–335. https://doi.org/10.1007/s11934-007-0080-y.

Philippe, M., Ranchon, F., Gilis, L., Schwiertz, V., Vantard, N., Ader, F., Labussiere-Wallet, H., Thomas, X., Nicolini, F.E., Wattel, E., Ducastelle-Leprêtre, S., Barraco, F., Lebras, L., Salles, G., Michallet, M., Rioufol, C., 2016. Cidofovir in the treatment of BK virus-associated hemorrhagic cystitis following allogeneic hematopoietic stem cell transplantation: a retrospective study and a literature review. Biol. Blood Marrow Transplant. 22, 723–730. https://doi.org/10.1016/j.bbmt.2015.12.009.

Pihusch, M., Bacigalupo, A., Szer, J., von Depka Prondzinski, M., Gaspar-Blaudschun, B., Hyveled, L., Brenner, B., 2005. For the F7BMT-1360 Trial Investigators, 2005. Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. J. Thromb. Haemost. 3, 1935–1944. https://doi.org/10.1111/j.1538-7836.2005.01523.x.

Rao, K.V., Buie, L.W., Shea, T., Gabriel, D.A., Comeau, T., Irons, R., Serody, J., Eron, B., Epstein, S., 2009. Intravesicular cidofovir for the management of BK virus-associated cystitis. Biol. Blood Marrow Transplant. 15, 391–392. https://doi.org/10.1016/j.bbmt.2008.12.490.

Roskopf, J., Fitzsimmons, W., Ahsan, N., Laskow, D., 2002. The pharmacologic treatment of human polyomavirus infection. Graft 5, 88–97. https://doi.org/10.1177/1522162802238461.

Russell, S.J., Vowels, M.R., Vale, T., 1994. Haemorragic cystitis in paediatric bone marrow transplant patients: an association with infective agents, GVHD, and prior cyclophosphamide. Bone Marrow Transplant. 13, 533–539.

Sakurada, M., Kondo, T., Umeda, M., Kawabata, H., Yamashita, K., Takori-Kondo, A., 2016. Successful treatment with intravesical cidofovir for virus-associated hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: a case report and a review of the literature. J. Infect. Chemother. 22, 495–500. https://doi.org/10.1016/j.jiac.2016.01.013.

Satyanarayana, G., Marty, F.M., Tan, C.S., 2014. The polyomavirus puzzle: is host immune response beneficial in controlling BK virus after adult hematopoietic cell transplantion? Transpl. Infect. Dis. 16 (4), 521–531.

Savona, M.R., Newton, D., Frame, D., Levine, J.T., Minesishi, S., Kaul, D.R., 2007. Low-dose cidofovir treatment of BK virus-associated hemorrhagic cystitis in recipients of hematopoietic stem cell transplant. Bone Marrow Transplant. 39, 783–787. https://doi.org/10.1038/sj.bmt.1705678.

Siegel, R.L., Miller, K.D., Jemal, A., 2017. Cancer statistics, 2017. CA Cancer J. Clin. 67, 7–30. https://doi.org/10.3322/caac.21387.

Tirindelli, M.C., Flammia, G., Sergi, F., Cerretti, R., Cudillo, L., Picardi, A., Postorino, M., Annibali, O., Greco, R., Avvisati, G., Arcese, W., 2009. Fibrin glue for refractory hemorrhagic cystitis after unrelated marrow, cord blood, and haploidentical hematopoietic stem cell transplantation. Transfusion 49, 170–175. https://doi.org/10.1111/j.1537-2995.2008.01934.x.

Tricco, A.C., Lillie, E., Zarin, W., O'Brien, K.K., Colquhoun, H., Levac, D., et al., 2018. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann. Intern. Med. 169 (7), 467–473. https://doi.org/10.7326/M18-0850.

Tsuboi, K., Kishi, K., Ohmachi, K., Yasuda, Y., Shimizu, T., Inoue, H., Matsumoto, M., Hattori, K., Yoshiba, F., Watanabe, S., Ogawa, Y., Kawada, H., Yabe, M., Kato, S., Hotta, T., 2003. Multivariate analysis of risk factors for hemorrhagic cystitis after hematopoietic stem cell transplantation. Bone Marrow Transplant. 32, 903–907. https://doi.org/10.1038/sj.bmt.1704240.

Tzannou, I., Papadopoulou, A., Naik, S., Leung, K., Martinez, C.A., Ramos, C.A., Carrum, G., Sasa, G., Lulla, P., Watanabe, A., Kuvalekar, M., Gee, A.P., Wu, M.F., Liu, H., Grilley, B.J., Krance, R.A., Gottschalk, S., Brenner, M.K., Rooney, C.M., Heslop, H.E., Leen, A.M., Omer, B., 2017. Off-the-shelf virus-specific t cells to treat bk virus, human herpesvirus 6, cytomegalovirus, epstein-barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. J. Clin. Oncol. 35, 3547–3557. https://doi.org/10.1200/JCO.2017.73.0655.

Vose, J.M., Reed, E.C., Pippert, G.C., Anderson, J.R., Bierman, P.J., Kessinger, A., Spinolo, J., Armitage, J.O., 1993. Mesna compared with continuous bladder irrigation as uroprotection during high-dose chemotherapy and transplantation: a randomized trial. J. Clin. Oncol. 11, 1306–1310. https://doi.org/10.1200/JCO.1993.11.7.1306.

Xu, L.P., Zhang, H.Y., Huang, X.J., Liu, K.Y., Liu, D.H., Han, W., Chen, H., Chen, Y.H., Gao, Z.Y., Zhang, Y.C., Lu, D.P., 2007. Hemorrhagic cystitis following hematopoietic stem cell transplantation: incidence, risk factors and association with CMV reactivation and graft-versus-host disease. Chin. Med. J. 120, 1666–1671.