BJUI
BJU International

Review

Chemical- and radiation-induced haemorrhagic cystitis: current treatments and challenges

Heather Payne[1], Andrew Adamson[2], Amit Bahl[3], Jonathan Borwell[4], David Dodds[5], Catherine Heath[6], Robert Huddart[7], Rhona McMenemin[8], Prashant Patel[9], John L. Peters[10] and Andrew Thompson[11]

[1]University College Hospital, London, [2]Hampshire Hospitals NHS Foundation Trust, [3]Bristol Oncology and Haematology Centre, Bristol, [4]Frimley Park Hospital NHS Foundation Trust, Surrey, [5]Beatson West of Scotland Cancer Care, Glasgow, [6]Southampton General Hospital, Southampton, [7]The Royal Marsden, Sutton, [8]Northern Centre for Cancer Treatment, Newcastle, [9]University Hospital, Birmingham, [10]Whipps Cross Hospital, Barts Health NHS Trust, London, UK, and [11]Wrightington, Wigan and Leigh NHS Foundation Trust, Wigan, UK

- To review the published data on predisposing risk factors for cancer treatment-induced haemorrhagic cystitis (HC) and the evidence for the different preventive and therapeutic measures that have been used in order to help clinicians optimally define and manage this potentially serious condition.
- Despite recognition that HC can be a significant complication of cancer treatment, there is currently a lack of UK-led guidelines available on how it should optimally be defined and managed.
- A systematic literature review was undertaken to evaluate the evidence for preventative measures and treatment options in the management of cancer treatment-induced HC.
- There is a wide range of reported incidence due to several factors including variability in study design and quality, the type of causal agent, the grading of bleeding, and discrepancies in definition criteria.
- The most frequently reported causal factors are radiotherapy to the pelvic area, where HC has been reported in up to 20% of patients, and treatment with cyclophosphamide and bacillus Calmette-Guérin, where the incidence has been reported as up to 30%.
- Mesna (2-mercaptoethane sodium sulphonate), hyperhydration and bladder irrigation have been the most frequently used prophylactic measures to prevent treatment-related cystitis, but are not always effective.
- Cranberry juice is widely cited as a preventative measure and sodium pentosanpolysulphate as a treatment, although the evidence for both is very limited.
- The best evidence exists for intravesical hyaluronic acid as an effective preventative and active treatment, and for hyperbaric oxygen as an equally effective treatment option.
- The lack of robust data and variability in treatment strategies used highlights the need for further research, as well as best practice guidance and consensus on the management of HC.

Keywords

radiation cystitis, chemical cystitis, haemorrhagic cystitis, sodium hyaluronate, hyperbaric oxygen

Introduction

Haemorrhagic cystitis (HC) can be either acute or chronic, and be caused by chemotherapeutic drugs, radiation therapy (RT), or exposure to chemicals, e.g. dyes or insecticides [1]. In transplantation settings, HC is typically associated with haematopoietic stem cell transplant (HSCT), but can also occur, albeit rarely, in solid organ recipients [2]. It is thought that a defect in the glycosaminoglycan (GAG) layer, which coats the uroepithelium and provides the initial barrier for physiological protection, may be the first step in its development [3]. Once injured or defective, the GAG layer loses its barrier properties, becomes permeable, and allows the inflammatory and hypersensitisation cycle to thrive [3].

With a tendency towards more aggressive treatment of cancer, including the use of HSCT, chemical- and RT-induced HC can be considered an increasingly important clinical issue, not least because it is a challenging condition to treat. However, few epidemiological studies have been undertaken and

 | doi:10.1111/bju.12291 *BJU Int* 2013; **112:** 885–897

therefore, the exact prevalence is unknown. Treatment can be problematic, especially in elderly patients who may be frail and have comorbidities [4], and because the condition often responds inadequately to the usual symptomatic therapies. In severe cases, HC is associated with significant morbidity, prolonged hospitalisation and occasional mortality, and may require more aggressive measures, e.g. supravesical urinary diversion, vesical artery selective embolization, and cystectomy [5]. Furthermore, as the global burden of cancer is forecast to rise, primarily due to ageing and growth of the world's population [6], it is likely that the incidence of HC will rise too because of the increasing use of RT and chemotherapy. However, there is currently a lack of consensus about the best treatment for patients with chemical- and RT-induced HC, as well as a lack of UK-led guidelines available on how it should optimally be defined and managed.

The aim of the present article is to review the predisposing risk factors for chemical- and RT-induced HC and the evidence for the different therapeutic and preventive measures that have been used to help clinicians better manage this potentially disabling condition.

Methods

A comprehensive literature search was undertaken in PubMed to retrieve studies and case reports, published in English, relating to the treatment of chemical- and RT-induced HC from 1980 to September 2012. The search was conducted using a comprehensive search strategy, including the terms 'haemorrhagic cystitis', 'chemical cystitis', 'radiation cystitis' in combination with 'risk factors', 'chemotherapeutic drugs', 'hyaluronic acid', 'sodium hyaluronate', 'hyperbaric oxygen', 'mesna', 'hyperhydration', 'bladder irrigation', 'pentosanpolysulphate', 'oestrogen', 'recombinant factor VII', 'formalin', and 'prostaglandin'. The search results were supplemented by review of the bibliographies of key articles for additional studies, inclusion of relevant abstracts presented at key meetings, as well as expert input, to help ensure the capture of all pertinent data.

Results

Incidence and Reported Predisposing Risk Factors

HC has multiple potential causes, including chemical toxins and radiation. As well as variability in the propensity of the causative factor to induce HC, differences in definition criteria are in part responsible for the wide range of reported incidences [7], with some degree of HC affecting up to 100% of patients in some studies. The available scoring systems for the severity of toxicity also use variable criteria, further complicating the comparative assessment of agents and studies in which they are used.

HC has a spectrum of manifestations that range from non-visible (or microscopic) haematuria to gross (visible) haematuria with clots, and can be graded as mild, moderate or severe according to the degree of pain and amount of haematuria [8]. A more comprehensive grading system for the severity of HC has been proposed by Droller et al. [9] (Table 1) and is used in many of the clinical trials presented. In rare cases it may be severe and life-threatening, requiring cystectomy [10]. Although most studies focus on severe (grades III–IV) HC, grade I HC can cause disabling symptoms, e.g. frequency, urgency and pelvic pain, often localised to the bladder or urethra.

Chemical-induced HC

A wide variety of chemotherapeutic drugs may cause chemical-induced HC (Table 2), most significantly the oxazaphosphorine compounds, cyclophosphamide [11–13] and ifosfamide [14,15]. Cyclophosphamide is used in the treatment of B cell malignant diseases and some solid tumours, conditioning before bone marrow transplantation, and in the treatment of certain immuno-inflammatory conditions, e.g. Wegener's granulomatosis, rheumatoid arthritis and systemic lupus erythematosus [1,4]. The cause of bladder damage has been linked to acrolein, a urinary metabolite of cyclophosphamide and ifosfamide [16]. HC can develop weeks or months after treatment in 20–25% of patients who receive high-dose cyclophosphamide [17]. However, ifosfamide has a greater tendency to produce this complication possibly because of the generally higher doses administered, which result in higher amounts of acrolein and the additional excretion of chloroacetaldehyde [14].

Table 1 Grading of HC as defined by Droller et al. [9].

Grade	Symptoms
I	Non-visible haematuria
II	Macroscopic haematuria
III	Macroscopic haematuria with small clots
IV	Gross haematuria with clots causing urinary tract obstruction requiring instrumentation for clot evacuation

Table 2 Frequently reported causes of chemical- and RT-induced HC.

Chemotherapeutic agents	Busulfan
	Cyclophosphamide
	Idarubicin
	Ifosfamide
	Paclitaxel/carboplatin therapy
Intravesical chemotherapy	Doxorubicin
	Epirubicin
	Mitomycin C
Other therapeutic agents and environmental toxins	BCG
	Gentian violet
	Ketamine hydrochloride
	Tiaprofenic acid
	Topical agents
RT	Including brachytherapy

Early-onset HC has been linked to toxic effects of chemo-irradiative agents used in the conditioning regimen for HSCT, e.g. cyclophosphamide and busulfan, and usually starts within 48–72 h after their use [1,18]. There is a wide range of reported incidence of chemotherapy-induced HC, from <10% to 35% [19–21]. In a retrospective, single-centre survey of 834 patients who underwent allogeneic stem cell transplantation, Grades II–V and III–V HC, according to the NCI Common Terminology Criteria for Adverse Events [22], developed in 13.1% and 3.2% of patients, respectively. HC started on a median (range) of 35 (0-166) days after transplant and persisted for 23 (2–270) days [23]. Clinical data also show that different conditioning regimens [24–26] and type of malignancy [27] may affect the development of HC. In a meta-analysis of 18 comparative studies totalling 3172 patients, the busulfan/cyclophosphamide regimen was associated with higher rates of HC than the total body irradiation-cyclophosphamide regimen [24]. Interestingly, in a multivariate analysis by Tsuboi et al. [19], prophylactic administration of 2-mercaptoethane sodium sulphonate (mesna) ($P = 0.01$) and bladder irrigation ($P < 0.001$) increased early-onset HC after stem cell transplantation by an odds ratio of 5.5 ($P = 0.01$) and 9.5-times ($P < 0.001$), respectively.

Several other anti-cancer drugs can result in urothelial GAG loss [28]. BCG is currently regarded as the most effective intravesical treatment for superficial TCC, and is also given to reduce recurrence and progression rates after surgical debulking or removal of more extensive tumours. However, cystitis is a common side-effect, occurring in ≈80% of BCG-treated patients [29], while haematuria occurs in an estimated 20%, and LUTS in an estimated 71% of patients receiving maintenance BCG [30]. In a review of the evidence supporting the need for maintenance BCG, cases of cystitis and the perceived risk of adverse events, including cystitis, were both cited as reasons for poor compliance and early discontinuation of therapy [29]. This finding is particularly important for patient management when one considers that patients who fail BCG maintenance therapy will often go on to require radical cystectomy for ultimate management of their bladder cancer [31].

Cases of HC have also been reported with the use of other therapeutic agents, recreational drugs and environmental toxins, including intravesical chemotherapy with doxorubicin, epirubicin and mitomycin C [32,33], tiaprofenic acid [34,35], gentian violet [36], ketamine [37], and less commonly, with exposure to certain industrial chemicals, e.g. the pesticide chlorodimeform [38], and topical agents [1].

RT-induced HC

Radiation to the pelvic area can result in both acute and chronic bladder injuries [39], and can lead to RT-induced HC, which is a potentially devastating side-effect that develops in a small but significant proportion of the treated population (≈5–10%) [40]. However, the incidence depends on the series, grading system and the method of calculation that have been used [40]. RT-induced HC can occur long after RT has ended, from 2 months to 15 years later [41]. In the BC2001 study, late toxicity was measured with the Radiation Therapy Oncology Group (RTOG) and Late Effects of Normal Tissue (Subjective, Objective, and Management elements) (LENT/SOM) criteria in 360 patients with muscle-invasive bladder cancer, who were treated either with RT, or RT plus chemotherapy (fluorouracil and mitomycin C). Grade 3 or 4 LENT/SOM genitourinary toxicity (excluding sexual dysfunction) occurred in 16.0% of RT- and 16.9% of chemoradiotherapy-treated patients at 1 year [42]. While Grade 3 or 4 RTOG toxicity occurred in only 3.3% and 1.3% of patients, respectively, all these adverse events concerned genitourinary symptoms [42].

The clinical manifestations of late RT HC include urinary frequency, urgency, dysuria, haematuria, reduced bladder capacity, sphincter dysfunction, reduced bladder capacity, and bladder perforation [40]. Severe manifestations of the condition can result in surgical procedures, e.g. urinary diversion, with or without cystectomy [43]. The pathogenesis of RT-induced cystitis originates as a progressive obliteration of the small blood vessels of the bladder wall with consequent development of hypoxia and tissue damage [41].

Prevention and Treatment of HC

Hyperhydration and Continuous Bladder Irrigation

Mesna, hyperhydration and bladder irrigation appear to be the most frequently used prophylactic measures for treatment-related HC, with varying, often disappointing, results [44–52] (Table 3). For continuous bladder irrigation, it is vital that clots are evacuated before therapy as the success of subsequent irrigation often depends upon the thoroughness of this procedure [5].

Turkeri et al. [45] reported that continuous bladder irrigation significantly decreased the frequency of HC in patients receiving busulfan and cyclophosphamide as a preparative regimen for bone marrow transplant (BMT) compared with no bladder irrigation (23% vs 53%, respectively; $P < 0.004$). Similar findings were reported by Hadjibabaie et al. [44] in a non-randomised, controlled study of HSCT patients who received mesna, hydration, and alkalisation regimens. HC occurred in fewer patients who received continuous bladder irrigation than in those who did not (32% vs 50%, respectively; $P = 0.11$). Continuous bladder irrigation was also found to significantly reduce the mean duration of HC (10 vs 18 days; $P = 0.02$) and the duration of hospitalisation (30.2 vs 39.6 days; $P < 0.001$) [44]. In a study by Trotman et al. [49], the overall incidence of HC in HSCT patients using a prophylactic regimen of hyperhydration and forced diuresis was 18.2%.

Table 3 Summary of the key studies for bladder irrigation, hyperhydration and forced diuresis and mesna in the prevention of chemical- and RT-induced cystitis.

Author	Study design	Patients, n	Treatment	Incidence of HC,% (P-value)	Adverse effects, % (P-value)
Bladder irrigation					
Hadjibabaie et al. (2008) [44]	Non-randomised, controlled	HSCT patients, 40	Bladder irrigation vs no bladder irrigation	32 vs 50 (NS)	UTI: 32.5 vs 20.0 (NS)
Turkeri et al. (1995) [45]	Retrospective	HSCT patients, 199	Bladder irrigation vs no bladder irrigation	23 vs 53 (<0.004)	UTI: 16.0 vs 14.0 (NS) Moderate to severe discomfort and bladder spasms: 6.0 (NS)
Atkinson et al. (1991) [48]	Prospective, randomised	BMT patients, 22	Bladder irrigation vs no bladder irrigation	48 vs 29* 52 vs 38† (NS, irrigation vs no irrigation)	Not reported
Hyperhydration and forced diuresis					
Trotman et al. (1999) [49]	Prospective	HSCT or BMT patients, 681	Hyperhydration and forced diuresis	HC: 18.2 Grade 3 or 4: 3.4	Not reported
Mesna					
Murphy et al. (1994) [50]	Retrospective	BMT patients, 227	Hyperhydration + mesna vs hyperhydration alone	16 vs 8 (0.08)	One patient receiving hyperhydration alone developed a bladder perforation, requiring surgical repair
Vose et al. (1993) [52]	Prospective, randomised	BMT patients, 200	Mesna vs bladder irrigation	18 vs 18 (NS)‡	UTI: 14 vs 27 (0.03)
Shepherd et al. (1991) [51]	Randomised	BMT patients, 100	Mesna vs hyperhydration	33 vs 20 (NS)	No unexpected toxicities

*NS, not statistically significant. *Patients receiving busulfan + cyclophosphamide + RT or cyclophosphamide + RT; †Patients receiving busulfan + cyclophosphamide; ‡Grade III/IV haematuria.*

Grade III or IV HC, based on the system devised by Droller et al. [9], occurred in 3.4% of patients. Of potential significance, a randomised study by Atkinson et al. [48] showed that bladder irrigation did not minimise the risk of HC in patients receiving allogeneic BMT as a treatment for haematological malignancy.

Mesna

Other routine methods of preventing chemical-induced HC include the use of mesna, which was specifically developed to bind acrolein in the urine. Mesna has been extensively investigated in the management of cyclophosphamide- and ifosfamide-induced HC with variable results [15,50–57]. It is also unclear whether the addition of mesna therapy to hyperhydration provides greater protection in BMT patients who are exposed to cyclophosphamide. Shepherd et al. [51] concluded that both approaches were equally effective in preventing cyclophosphamide-induced HC in BMT patients. Nevertheless, HC was still seen in 33% of patients who received mesna prophylaxis [51]. Similar findings were reported by Vose et al. [52] in a prospective randomised trial of mesna and continuous bladder irrigation. Whilst the overall incidence of haematuria of any grade was significantly higher in the bladder-irrigation group compared with the mesna group (76% vs 53%; $P = 0.007$), the incidence of grade III and IV haematuria was the same in both treatment groups (18%; statistically non-significant) [52]. Less convincing data were reported by Murphy et al. [50] who failed to show a benefit in adding mesna to hyperhydration in preventing cyclophosphamide-induced HC. Other authors have also found that mesna prophylaxis does not completely prevent bladder damage [15] and possibly has a toxic effect on bladder mucosa [19].

Intravesical Therapy

Despite prophylactic hyperhydration, continuous bladder irrigation or use of mesna, some BMT patients may have refractory HC and require alternative treatment regimens [58]. Several intravesical therapies have been evaluated including chondroitin sulphate, sodium hyaluronate, prostaglandins (PGE_1 PGE_2, and $PGF_{2\alpha}$), formalin, and alum irrigation (Table 4) [58–68].

Chondroitin sulphate

Most of the published studies on the use of chondroitin sulphate have evaluated its use in the treatment of interstitial cystitis/painful bladder syndrome. Based on animal studies, Hazewinkel et al. [59] hypothesised that prophylactic installation of chondroitin sulphate in patients undergoing RT for gynaecological malignancies may limit the risk of RT cystitis symptoms. In their pilot study, the efficacy of chondroitin sulphate was evaluated in 20 patients; 10 received weekly intravesical installations and 10 were controls. The acceptability of instillations and bladder pain were evaluated using a visual analogue scale (VAS). The patients receiving chondroitin sulphate reported less bothersome symptoms and the treatment was well tolerated. The instillations also appeared to reduce overactive bladder symptoms during the

Table 4 Summary of the key studies on intravesical therapy used in chemical- and RT-induced cystitis.

Author	Study design	Patients, n	Treatment	Efficacy	Adverse effects
Chondroitin sulphate					
Hazewinkel et al. (2011) [59]	Comparative pilot	Patients with gynaecological malignancies undergoing RT, 20	Chondroitin sulphate vs no chondroitin sulphate	HC not reported. Trend towards less bothersome urogenital symptoms in treatment group	Well tolerated
Sodium hyaluronate					
Shao et al. (2012) [60]	Randomised	Patients with pelvic malignancies undergoing RT, 36	Sodium hyaluronate vs HBO	Complete response:† 6 months: 87.5% vs 75.0% 12 months: 75.0% vs 50.0% 18 months: 50.0% vs 45.0% (all NS) Decrease in voiding frequency: significant at 6 months in both groups ($P < 0.05$) and at 12 months for sodium hyaluronate ($P < 0.05$) VAS: significant improvement maintained for 18 months in both groups.	UTI: 42.8% vs 10.0% in first 6 months ($P = 0.034$) NS at 12 and 18 months
Sommariva et al. (2010) [61]	Prospective	Consecutive patients with cystitis receiving CT for bladder cancer or RT for prostate cancer, 69	Sodium hyaluronate	After 4 weeks, bladder capacity increased in all patients, and urgency and pain disappeared. 97% reported complete relief of dysuria and pain	No adverse effects observed
Delgado et al. (2003) [62]	Retrospective	Consecutive patients with cervix/uterine cancer undergoing RT, 90	Standard of care vs standard of care alone plus sodium hyaluronate	RT toxicity:* Week 4: 1.33 vs 0.71 ($P < 0.005$) End of RT: 1.24 vs 0.71 ($P < 0.004$)	Not reported
Samper Ots et al. (2009) [63]	Retrospective	Patients with acute vesical toxicity caused by BT, 95	Sodium hyaluronate vs no sodium hyaluronate	Over whole study period, vesical toxicity significantly lower for sodium hyaluronate (2.08% vs 12.8%; $P < 0.05$)	No related adverse effects
Prostaglandin					
Ippoliti et al. (1995) [58]	Case series	BMT patients with grade III or IV HC, 24	Prostaglandin $F_{2\alpha}$	62% had total response with doses ≥0.8 mg/dL 9 (37.5%) patients relapsed at median of 7 days	95.8% had bladder spasms
Levine et al. (1993) [64]	Case series	BMT patients, 16 and patients with cancer, 2 with HC after CYC treatment	Prostaglandin $F_{2\alpha}$	50% had complete reduction in gross haematuria 3 cases of recurrent haematuria	78.0% had bladder spasms
Formalin					
Lojanapiwat et al. (2002) [65]	Case series	Patients with pelvic malignancies and intractable haemorrhage secondary to RT-induced cystitis, 11	4% formalin	82% had complete response	4 major complications (e.g. anuria, fistula) and several minor (e.g. fever, tachycardia) complications
Dewan et al. (1993) [66]	Retrospective review	Patients with cervical cancer with HC after RT, 35	1% formalin	89% had complete response and 8% partial response	Major complications in 11%, with 5 requiring subsequent urinary diversion. Probable formalin toxicity in 1 patient
Vicente et al. (1990) [67]	Retrospective review	Patients with HC after CYC or RT, 25	4% formalin	88% had good result	1 case of upper urinary tract dilatation
Alum irrigation					
Ho et al. (2009) [68]	Case report	Patient with ovarian cancer and HC after RT	1% alum	Haematuria stopped after 24 h	Well tolerated

*CT, chemotherapy; CYC, cyclophosphamide; BT, brachytherapy; NS, not statistically significant; *Toxicity assessed using RTOG/EORTC Radiation Toxicity Score; †Complete response defined as the day when the symptoms improved.*

period of RT. These findings support those of an earlier multi-national, multicentre, prospective observational clinical trial of patients with chronic forms of cystitis associated with a possible GAG layer deficit, including RT-induced cystitis [69]. However, larger trials are required to specifically assess the evidence in support of the prophylactic use of chondroitin sulphate in patients undergoing RT.

Sodium hyaluronate

Sodium hyaluronate, a derivative of hyaluronic acid, has been developed to temporarily replenish the deficient GAG layer [7] and has been used successfully in the treatment of refractory interstitial cystitis [70,71] and more recently in preventing and treating chemical- and RT-induced HC [7,60–63,72–74]. Data from a retrospective study by Delgado et al. [62], which assessed toxicity using the RTOG/European Organisation for the Research and Treatment of Cancer (EORTC) Radiation Toxicity Score show that weekly instillations of sodium hyaluronate in patients receiving RT for gynaecological tumours decreased RT-induced toxicity. In a 5-year follow-up study, Samper Ots et al. [63] also found that, compared with no sodium hyaluronate, intravesical installation of hyaluronic acid before each brachytherapy session significantly reduced the incidence of RT-induced cystitis in patients with cervical and endometrial cancer after the second (20.8% vs 40.4%) and fourth session (10.9% vs 31.9%) ($P < 0.05$, for both comparisons). Over the whole study period, the percentage of patients presenting vesical toxicity of grade ≥2 was significantly lower in the sodium hyaluronate group (2.08% vs 12.8%; $P < 0.05$).

Further data from a prospective study by Sommariva et al. [61] show that sodium hyaluronate also relieves the symptoms of chemo- or RT-induced cystitis. In all, 69 consecutive patients who had symptoms of cystitis after RT for prostatic cancer or after intravesical BCG or mitomycin C were given intravesical instillations of sodium hyaluronate and cortisone. Overall, 67 (97%) patients reported complete relief of dysuria and pain, which was assessed using a VAS. Patients with chemical-induced cystitis were found to respond slightly better than those who had RT-induced cystitis. Shao et al. [60] have also shown that intravesical instillation of sodium hyaluronate is as effective as hyperbaric oxygen (HBO) therapy in the treatment of RT-induced cystitis. In this randomised study of 36 patients with pelvic malignancies, there was no statistical difference between the two groups in the improvement rate (complete response and partial response) at 6, 12 and 18 months after treatment. However, whilst the decrease in frequency vs baseline was significant in both groups 6 months after treatment, it was significant only in the sodium hyaluronate group 12 months after therapy. This treatment strategy was well tolerated and resulted in a sustained decrease of bladder bleeding, pelvic pain and frequency of voiding for ≥12 months [60].

Prostaglandin

Data from several published case series [58,64] and case reports [75–78] suggest that intravesical prostaglandins (PGE_1 PGE_2, and $PGF_{2\alpha}$) may be useful to prevent or treat HC secondary to RT or cyclophosphamide therapy. Although the exact mechanism of action is unclear, the prostaglandins may work by causing smooth muscle contraction of the blood vessels in the mucosa and submucosa, through membrane stabilisation, or by induction of haemostasis with platelet aggregation [58].

Ippoliti et al. [58] evaluated the use of a $F_{2\alpha}$ analogue in 24 adult BMT recipients with grade 3 or 4 HC who had received a conditioning regimen of cyclophosphamide administered with hyperhydration and mesna. Overall, 15 (63%) patients responded to treatment, with a median time to response of 3 days. However, nine of these patients (37.5%) had a recurrence of HC at a median of 7 days later. These results were comparable to other small series [64]. The main reported side-effect of prostaglandins appears to be the occurrence of bladder spasm [58,64].

Formalin

Intravesical formalin installation has been evaluated for the treatment of HC secondary to RT-induced cystitis [65–67] and cyclophosphamide therapy [67], and has been shown to be effective in controlling severe bladder haemorrhage after RT of the pelvis [65,67]. In a retrospective review of 35 patients with RT-induced HC, formalin therapy resulted in a complete response in 89% of patients [66]. However, treatment is dose-dependent [65]. There have also been reports of major complications (e.g. anuria, vesicle fistula) and minor complications (e.g. fever, transient tachycardia) after treatment, and recurrent haematuria, as well as probable fatal toxicity [65,66].

Alum irrigation

Alum irrigation was first reported in 1982, when it was successfully used to treat six patients with massive bladder haemorrhage secondary to RT cystitis, bladder carcinoma and HC [79]. Since then, there have been several reports on the use of alum irrigation in the management of cyclophosphamide- and RT-induced HC with varying degrees of success [68,80,81]. There have also been several case reports of aluminium toxicity after intravesical alum irrigation for HC in children [82–84]; therefore, vigilance is needed to avoid these toxic effects [68].

Systemic Treatments

Systemic treatments, e.g. HBO, oestrogen, sodium pentosanpolysulphate, recombinant factor VII or VIII, and aminocaproic acid have been used with some success in the treatment of HC (Table 5) [39,41,85–92].

Table 5 Summary of the key studies on systemic treatments used in chemical- and RT-induced cystitis.

Reference	Study design	Patients, n	Treatment	Efficacy	Adverse effects
HBO					
Nakada et al. (2012) [85]	Prospective	Patients with prostate cancer with CYC-induced HC, 38	HBO	High efficacy ratios of objective and subjective findings obtained at 2 and 4 (79–95%) years, respectively	Some patients complained of occasional otalgia during follow-up.
Vilar et al. (2011) [41]	Prospective	Patients with cancer with RT-induced HC, 38	HBO	75% response rate for patients presenting with severe haematuria. 94% global response rate after average follow-up of 36.3 months	Well tolerated 1 patient had an episode of barotrauma.
Oliai et al. (2012) [86]	Retrospective	Patients with RT-induced HC and proctitis, 19	HBO	81% complete response. 18% partial response. 36% recurrence after median 10 months.	Otalgia in 33%. No major adverse effects observed.
Davis et al. (2011) [87]	Retrospective review	Patients with CYC-induced HC, 6	HBO	All 6 responded after 14–40 HBO therapy sessions	1 patient had bilateral myringotomies to equalise pressure in middle ear.
Ajith Kumar et al. (2011) [88]	Case reports	Patients with CYC-induced HC, 2	HBO	Both patients responded after 19–36 sessions	No side-effects observed.
Mohamad Al-Ali et al. (2010) [89]	Retrospective review	Patients with different pelvic organ malignancies and RT-induced HC, 14	HBO vs no HBO	20% (3 of 14) response rate	No adverse effects observed.
Oestrogen					
Heath et al. (2006) [90]	Case series	HSCT children/adolescents with HC, 10	Conjugated oestrogen	80% significant improvement in haematuria 60% resolution of macroscopic haematuria	Generally well tolerated. Treatment interrupted in one patient (hepatotoxicity)
Ordemann et al. (2000) [91]	Case reports	HSCT and cancer patients with HC, 10	Conjugated oestrogen	50% resolution in patients with mild HC. 80% resolution in patients with severe HC	Generally well tolerated. Treatment interrupted in one patient (hepatotoxicity)
Sodium pentosanpolysulphate					
Sandhu et al. (2004) [39]	Retrospective	Patients with RT- or CYC-induced HC, 51	SPP	19.6% resolution of haematuria. 41% dose reduced to a maintenance dose.	No side-effects requiring discontinuation
Ashrani et al. (2006) [92]	Pilot	Patients with refractory chemotherapy-induced HC, 7	rFVIIa	85.7% response rate (57.1% complete; 28.6% partial). Response duration temporary	No serious adverse effects

CYC, cyclophosphamide; rFVIIa, recombinant factor VII; SPP, sodium pentosanpolysulphate.

HBO therapy

HBO therapy promotes capillary angiogenesis and the healing process in damaged tissue and has been extensively evaluated in the management of adults with RT-induced [41,85,86,93–97] and cyclophosphamide-induced [87,88,98] HC. Nakada et al. [85] and Oliai et al. [86] recently reported favourable outcomes in patients treated with HBO therapy for RT-induced HC. Similar findings were also reported in a prospective study by Vilar et al. [41]. In all, 14 patients received HBO treatment for the first time, whereas 24 had received previous treatment with HBO. After a mean (range) follow-up of 36.3 (12–60) months, haematuria was completely resolved in 36 (94.7%) patients [41]. Conversely, Mohamad Al-Ali et al. [89] found that few patients recovered from HC after HBO therapy. Furthermore, patients treated with HBO had a significantly lower cure rate of post-RT HC in comparison with patients who did not receive HBO.

Although much of the research has focussed on RT-induced cystitis, there have been several recent case reports on the use of HBO in the management of cyclophosphamide-induced HC. Davis et al. [87] reviewed the case records of six patients with life-threatening haemorrhage and reported that bleeding ceased in all patients after 14–40 treatments without complications. Similarly, Ajith Kumar et al. [88] retrospectively reviewed the case notes of two patients with drug-induced HC and reported that HBO therapy resulted in complete cessation of bleeding in both cases, with no side-effects noted during the course of therapy. There are also case reports concerning the successful use of HBO for intractable, refractory HC in patients with systemic lupus erythematosus [99] and Wegener's granulomatosis [100]

Oestrogen

Several small series and case reports have reported that HC secondary to RT or cyclophosphamide therapy has been successfully treated with oestrogen [90,91,101,102]. Heath et al. [90] reported that eight out of 10 children and adolescents treated initially with intravenous oestrogen and then oral oestrogen after 2 or 3 days had a significant reduction in their symptoms after commencing therapy. In another series, Ordemann et al. [91] reported that, after treatment with oral oestrogen, haematuria resolved in two of four adult patients with mild HC and four of five patients with severe HC. In all the case reports, oestrogen therapy appeared to be generally well tolerated [90,91,101,102]. Potential adverse effects of long-term exposure to oestrogens include an increased risk of cancer [91].

Sodium pentosanpolysulphate

Sodium pentosanpolysulphate is a semi-synthetic GAG similar to heparin with anticoagulant properties and fibrinolytic effects [5]. This treatment has had some success in small series and case reports in treating patients who have developed HC secondary to RT or cyclophosphamide therapy [103–105], but the patient series have been limited in size. In a larger study, Sandhu et al. [39] retrospectively reviewed the pharmacy records of 60 patients with HC; of these patients, 53 had received radical RT for pelvic malignancy and seven had received systemic cyclophosphamide. After treatment with sodium pentosanpolysulphate, the dose was gradually reduced in 21 patients and treatment was discontinued in a further 10 patients because the haematuria stopped completely. Although the safety and efficacy of sodium pentosanpolysulphate has not been established in paediatric patients [5], a recent retrospective case note review of children with HC after stem cell transplant/chemotherapy reported that early identification, avoidance of urethral catheterisation, and use of sodium pentosanpolysulphate significantly reduces blood transfusion requirements and mortality from HC [103].

Recombinant factor VIIa/factor XIII

Several case reviews and case reports have suggested a potential role for recombinant factor VII or XIII in the treatment of cyclophosphamide- and RT-induced HC [106–109]. Ashrani et al. [92] reported the results of a pilot study using high-dose activated recombinant factor VII in seven adult patients with severe refractory HC and prior exposure to cyclophosphamide or ifosfamide. Six of the seven patients achieved a response: four complete responses and two partial responses. Although there was no serious adverse event, the response duration was found to be only temporary. In a multicentre, randomised trial, Pihusch et al. [110] reported no aggregate benefit in the treatment of various haemorrhagic complications, including HC, with recombinant factor VII after HSCT, although *post hoc* analysis showed an improvement in the control of bleeding with increased dose.

Aminocaproic acid

Aminocaproic acid has proved to be successful in one small study of 37 patients with intractable bladder haemorrhage, most of whom had RT- or cyclophosphamide-induced cystitis. No side-effects were observed [111].

Other Therapeutic Approaches

Anecdotally, patients with chemical or RT-induced cystitis are often advised to try cranberry juice, and in some centres, it is considered the 'gold standard' of treatment. A recent systematic review and meta-analysis of 13 randomised controlled trials showed that cranberry-containing products are associated with a protective effect against UTIs [112]. The mechanism is thought to be the adhesion of bacteria to uroepithelial cells by proanthocyanidins, a compound present in cranberry [113]. Although earlier studies showed statistically insignificant or negative results [114,115], data from a recent study show that the beneficial effects of

cranberry extract in prevention of LUTS can be seen in patients with prostate cancer with acute bladder damage associated with high-dose RT [113]. The authors propose that because of its strong antioxidant properties, it is possible that cranberry could attenuate actinic damage to the bladder mucosa, reducing the inflammatory process and, as a consequence, its symptoms. However, further studies are warranted [113].

Over the last 15 years, numerous other therapeutic approaches have been tried and have shown some benefit in the treatment of HC. These include: botulinum toxin A bladder injections in patients with refractory RT-induced cystitis and BCG-induced chemical cystitis [116], intravesical recombinant human granulocyte-macrophage colony-stimulating factor [117], neodymium:YAG (yttrium-aluminium-garnet) laser therapy [118,119], and WF10 (tetrachlorodecaoxide i.v. solution) therapy [120]. However, the role of many of these treatment methods remains investigational.

Surgical Approaches to HC

In cases where medical treatment has failed to control HC, surgical intervention may be the treatment of last resort [1,121]. Several options have been used, including cutaneous ureterostomy [121], cystoscopy and diathermy [122], vesical artery embolization [123–125], and supravesical urinary diversion with, or without, radical cystectomy [43,126]. Although successful resolution after the various interventions has been reported in a limited number of case studies [10,121–125], major surgical procedures in these cases can be associated with high morbidity and mortality [125], as well as leading to permanent changes to the anatomy and function of the genitourinary system [10,127].

Discussion

HC remains a significant complication after high-dose chemo-RT, especially in conjunction with HSCT [7]. However, there is a wide range of reported incidence due to several factors including: the type of causal agent, the grading of bleeding, and discrepancies in definition criteria [7,23]. Although HC is a potentially severe complication, which can cause significant morbidity and considerable expense due to prolonged hospitalisation [18], there is no published national or international consensus on the optimal therapeutic strategy. The present review has highlighted that the evidence base is currently limited for the various treatment methods used to prevent and/or treat HC. Most of the reported studies are either uncontrolled, non-randomised studies, or small case series or case reports, and involve few patients who have had several different treatment methods. The two therapeutic approaches with seemingly the best available evidence are HBO therapy in the treatment of HC and sodium hyaluronate in the prevention and treatment of HC.

Several studies have evaluated the use of standard prophylactic measures, including bladder irrigation and the use of mesna, to reduce the risk of HC, but the results have been variable. While bladder irrigation and mesna have been shown to be effective in preventing HC [44,45], Tsuboi et al. [19] unexpectedly found that both these prophylactic measures increased the frequency of HC after HSCT, particularly when mesna was administered with busulfan. Therefore, it appears that the standard preventive protocols do not always satisfactorily protect the patient from bladder injury [128].

HBO therapy has been shown to have efficacy in the treatment of patients in whom other forms of management have failed, with few side-effects [39,86,87,97]; although the number of HBO treatments administered and characteristics of hyperbaric exposure differs among the various reports. A randomised controlled study on the use of HBO for the treatment of RT-induced HC is currently recruiting patients [129]. Whilst HBO therapy appears an effective treatment method for HC, the practicalities of longer-term administration and access/availability issues are potential barriers to its more widespread use.

In recent years, GAG-replenishment therapy has widened the therapeutic options for patients with HC [130]. Intravesical installation of sodium hyaluronate has been used successfully in the prevention and treatment of chemical- and RT-induced HC. Studies have shown that sodium hyaluronate can significantly relieve bleeding, pain and dysuria and is well tolerated [61–63,72]. Data from a small randomised study have shown that it is at least as effective as HBO at treating RT-induced HC [60]. The positive efficacy results and apparent lack of side-effects make sodium hyaluronate a potentially attractive option for the prevention and treatment of HC secondary to RT and chemotherapy, particularly in patients already catheterised.

Several other therapeutic and preventive measures have also been used in the treatment of HC, e.g. intravesical prostaglandins, chondroitin sulphate, oestrogen therapy, and sodium pentosanpolysulphate. Whilst there has been some reported success with these therapies [39,58,59,91], it is difficult to draw any firm conclusions due to the generally poor quality of the available evidence.

A systematic review and meta-analysis of interventions for preventing HC in patients undergoing HSCT is currently being undertaken by the Cochrane Collaboration and it is hoped that this will provide more conclusive evidence on the optimum treatment [131]. The lack of robust data and variability in treatment strategies used highlights the need for further research, as well as best practice guidance and consensus on the management of this complication, which can often be challenging to treat.

Acknowledgements

Writing and editorial support was provided by Strategen Limited, Basingstoke, UK.

Conflict of Interests

The authors received no financial support. All authors have previously served as advisors, speakers and/or investigators for Teva UK Limited and have received honoraria/research grants in this regard.

Funding

Teva UK Limited has provided arm's length funding to support the production of this article. Teva UK Limited did not initiate this article, and has had no input into the editorial content or the final article.

References

1 **Manikandan R, Kumar S, Dorairajan LN.** Hemorrhagic cystitis: a challenge to the urologist. *Indian J Urol* 2010; 26: 159–66

2 **Hassan Z.** Management of refractory hemorrhagic cystitis following hematopoietic stem cell transplantation in children. *Pediatr Transplant* 2011; 15: 348–61

3 **Bassi PF, Costantini E, Foley S, Palea S.** Glycosaminoglycan therapy for bladder diseases: emerging new treatments. *Eur Urol Suppl* 2011; 10: 451–9

4 **Mukhtar S, Woodhouse C.** The management of cyclophosphamide-induced haematuria. *BJU Int* 2010; 105: 908–12

5 **Decker DB, Karam JA, Wilcox DT.** Pediatric hemorrhagic cystitis. *J Pediatr Urol* 2009; 5: 254–64

6 **Cancer Research UK.** World cancer factsheet. Available at: http://publications.cancerresearchuk.org/downloads/product/CS_FS_WORLD_A4.pdf. Accessed September 2012

7 **Miodosky M, Abdul-Hai A, Tsirigotis P et al.** Treatment of post-hematopoietic stem cell transplantation hemorrhagic cystitis with intravesicular sodium hyaluronate. *Bone Marrow Transplant* 2006; 38: 507–11

8 **El-Zimaity M, Saliba R, Chan K et al.** Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: donor type matters. *Blood* 2004; 103: 4674–80

9 **Droller MJ, Saral R, Santos G.** Prevention of cyclophosphamide-induced hemorrhagic cystitis. *Urology* 1982; 20: 256–8

10 **Garderet L, Bittencourt H, Sebe P et al.** Cystectomy for severe hemorrhagic cystitis in allogeneic stem cell transplant recipients. *Transplantation* 2000; 70: 1807–11

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

12 **Sandoval C, Swift M.** Treatment of lymphoid malignancies in patients with ataxia-telangiectasia. *Med Pediatr Oncol* 1998; 31: 491–7

13 **Le Guenno G, Mahr A, Pagnoux C, Dhote R, Guillevin L, French Vasculitis Study Group.** Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. *Arthritis Rheum* 2011; 63: 1435–45

14 **Klatersky J.** Side effects of ifosfamide. *Oncology* 2003; 65 (Suppl. 2): 7–10

15 **Lima MV, Ferreira FV, Macedo FY, de Castro Brito GA, Ribeiro RA.** Histological changes in bladders of patients submitted to ifosfamide chemotherapy even with mesna prophylaxis. *Cancer Chemother Pharmacol* 2007; 59: 643–50

16 **Korkmaz A, Topal T, Oter S.** Pathophysiological aspects of cyclophosphamide and ifosfamide induced hemorrhagic cystitis; implication of reactive oxygen and nitrogen species as well as PARP activation. *Cell Biol Toxicol* 2007; 23: 303–12

17 **Emadi A, Jones RJ, Brodsky RA.** Cyclophosphamide and cancer: golden anniversary. *Nat Rev Clin Oncol* 2009; 6: 638–47

18 **Xu LP, Zhang HY, Huang XJ et al.** Hemorrhagic cystitis following hematopoietic stem cell transplantation: incidence, risk factors and association with CMV reactivation and graft-versus-host disease. *Chin Med J (Engl)* 2007; 120: 1666–71

19 **Tsuboi K, Kishi K, Ohmachi K et al.** Multivariate analysis of risk factors for hemorrhagic cystitis after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; 32: 903–7

20 **Tang W, Wang L, Zhao WL, Chen YB, Shen ZX, Hu J.** Intravenous busulfan-cyclophosphamide as a preparative regimen before allogeneic hematopoietic stem cell transplantation for adult patients with acute lymphoblastic leukemia. *Biol Blood Marrow Transplant* 2011; 17: 1555–61

21 **Carpenter PA, Marshall GM, Giri N, Vowels MR, Russell SJ.** Allogeneic bone marrow transplantation for children with acute lymphoblastic leukemia conditioned with busulfan, cyclophosphamide and melphalan. *Bone Marrow Transplant* 1996; 18: 489–94

22 **NCI.** Common terminology criteria for adverse events, v3.0 (CTCAE), 2003. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed June 2013

23 **Hassan Z, Remberger M, Svenberg P et al.** Hemorrhagic cystitis: a retrospective single-center survey. *Clin Transplant* 2007; 21: 659–67

24 **Shi-Xia X, Xian-Hua T, Hai-Qin X, Bo F, Xiang-Feng T.** Total body irradiation plus cyclophosphamide versus busulphan with cyclophosphamide as conditioning regimen for patients with leukemia undergoing allogeneic stem cell transplantation: a meta-analysis. *Leuk Lymphoma* 2010; 51: 50–60

25 **Ringdén O, Labopin M, Tura S et al.** A comparison of busulphan versus total body irradiation combined with cyclophosphamide as conditioning for autograft or allograft bone marrow transplantation in patients with acute leukaemia. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Br J Haematol* 1996; 93: 637–45

26 **Ringdén O, Ruutu T, Remberger M et al.** A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: a report from the Nordic Bone Marrow Transplantation Group. *Blood* 1994; 83: 2723–30

27 **Sencer SF, Haake RJ, Weisdorf DJ.** Hemorrhagic cystitis after bone marrow transplantation. Risk factors and complications. *Transplantation* 1993; 56: 875–9

28 **Lazzeri M, Montorsi F.** The therapeutic challenge of 'chronic cystitis': search well, work together, and gain results. *Eur Urol* 2011; 60: 78–80

29 **Lamm D, Persad R, Colombel M, Brausi M.** Maintainance Bacillus Calmette-Guérin: the standard of care for the prophylaxis and management of intermediate- and high-risk non-muscle-invasive bladder cancer. *Eur Urol Suppl* 2010; 9: 715–34

30 **Hall MC, Chang SS, Dalbagni G et al.** Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol* 2007; 178: 2314–30

31 **Soloway MS, Hepps D, Katkoori D, Ayyathurai R, Manoharan M.** Radical cystectomy for BCG failure: has the timing improved in recent years? *BJU Int* 2011; 108: 182–5

32 **Isaka S, Okano T, Abe K, Shimazaki J.** Sequential instillation therapy with mitomycin C and adriamycin for superficial bladder cancer. *Cancer Chemother Pharmacol* 1992; 30 (Suppl.): S41–4

33 **Witjes JA, Caris CT, Mungan NA, Debruyne FM, Witjes WP.** Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guerin versus mitomycin C alone in patients with superficial bladder cancer. *J Urol* 1998; 160: 1668–71

34 **Crawford ML, Waller PC, Wood SM.** Severe cystitis associated with tiaprofenic acid. *Br J Urol* 1997; 79: 578–84

35 **Buchbinder R, Forbes A, Kobben F, Boyd I, Snow RM, McNeil JJ.** Clinical features of tiaprofenic acid (surgam) associated cystitis and a study of risk factors for its development. *J Clin Epidemiol* 2000; 53: 1013–9

36 **Kim SJ, Koh DH, Park JS, Ahn HS, Choi JB, Kim YS.** Hemorrhagic cystitis due to intravesical instillation of gentian violet completely recovered with conservative therapy. *Yonsei Med J* 2003; 44: 163–5

37 **Chen CH, Lee MH, Chen YC, Lin MF.** Ketamine-snorting associated cystitis. *J Formos Med Assoc* 2011; 110: 787–91

38 **Folland DS, Kimbrough RD, Cline RE, Swiggart RC, Schaffner W.** Acute hemorrhagic cystitis. Industrial exposure to the pesticide chlordimeform. *JAMA* 1978; 239: 1052–5

39 **Sandhu SS, Goldstraw M, Woodhouse CR.** The management of haemorrhagic cystitis with sodium pentosan polysulphate. *BJU Int* 2004; 94: 845–7

40 **Denton AS, Clarke N, Maher J.** Non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database Syst Rev* 2002; (3)CD001773

41 **Vilar DG, Fadrique GG, Martín IJ et al.** Hyperbaric oxygen therapy for the management of hemorrhagic radio-induced cystitis. *Arch Esp Urol* 2011; 64: 869–74

42 **James ND, Hussain SA, Hall E et al.** Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012; 366: 1477–88

43 **Smit SG, Heyns CF.** Management of radiation cystitis. *Nat Rev Urol* 2010; 7: 206–14

44 **Hadjibabaie M, Alimoghaddam K, Shamshiri AR et al.** Continuous bladder irrigation prevents hemorrhagic cystitis after allogeneic hematopoietic cell transplantation. *Urol Oncol* 2008; 26: 43–6

45 **Turkeri LN, Lum LG, Uberti JP et al.** Prevention of hemorrhagic cystitis following allogeneic bone marrow transplant preparative regimens with cyclophosphamide and busulfan: role of continuous bladder irrigation. *J Urol* 1995; 153: 637–40

46 **Rosenzweig MQ, Schaefer PM, Rosenfeld CS.** Prevention of transplant-related hemorrhagic cystitis using bladder irrigation with sorbitol. *Bone Marrow Transplant* 1994; 14: 491–2

47 **Meisenberg B, Lassiter M, Hussein A, Ross M, Vredenburgh JJ, Peters WP.** Prevention of hemorrhagic cystitis after high-dose alkylating agent chemotherapy and autologous bone marrow support. *Bone Marrow Transplant* 1994; 14: 287–91

48 **Atkinson K, Biggs JC, Golovsky D et al.** Bladder irrigation does not prevent haemorrhagic cystitis in bone marrow transplant recipients. *Bone Marrow Transplant* 1991; 7: 351–4

49 **Trotman J, Nivison-Smith I, Dodds A.** Haemorrhagic cystitis: incidence and risk factors in a transplant population using hyperhydration. *Bone Marrow Transplant* 1999; 23: 797–801

50 **Murphy C, Harden E, Stevens D, Lynch J, Montes V, Herzig R.** The addition of mesna to hyperhydration does not decrease the incidence of hemorrhagic cystitis in patients receiving high-dose cyclophosphamide. *Oncol Rep* 1994; 1: 265–6

51 **Shepherd JD, Pringle LE, Barnett MJ, Klingemann HG, Reece DE, Phillips GL.** Mesna versus hyperhydration for the prevention of cyclophosphamide-induced hemorrhagic cystitis in bone marrow transplantation. *J Clin Oncol* 1991; 9: 2016–20

52 **Vose JM, Reed EC, Pippert GC et al.** Mesna compared with continuous bladder irrigation as uroprotection during high-dose chemotherapy and transplantation: a randomized trial. *J Clin Oncol* 1993; 11: 1306–10

53 **Katz A, Epelman S, Anelli A et al.** A prospective randomized evaluation of three schedules of mesna administration in patients receiving an ifosfamide-containing chemotherapy regimen: sustained efficiency and simplified administration. *J Cancer Res Clin Oncol* 1995; 121: 128–31

54 **Mace JR, Keohan ML, Bernardy H et al.** Crossover randomized comparison of intravenous versus intravenous/oral mesna in soft tissue sarcoma treated with high-dose ifosfamide. *Clin Cancer Res* 2003; 9: 5829–34

55 **Khojasteh NH, Zakerinia M, Ramzi M, Haghshenas M.** A new regimen of MESNA (2-mercaptoethanesulfonate) effectively prevents cyclophosphamide-induced hemorrhagic cystitis in bone marrow transplant recipients. *Transplant Proc* 2000; 32: 596

56 **Frustaci S, Foladore S, De Pascale A et al.** Feasibility and efficacy of arginine 2-mercaptoethanesulfonate (ARGIMESNA) in the prevention of hemorragic cystitis from ifosfamide (IFO). *Ann Oncol* 1992; 3 (Suppl. 2): S115–8

57 **Letendre L, Hoagland HC, Gertz MA.** Hemorrhagic cystitis complicating bone marrow transplantation. *Mayo Clin Proc* 1992; 67: 128–30

58 **Ippoliti C, Przepiorka D, Mehra R et al.** Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. *Urology* 1995; 46: 811–5

59 **Hazewinkel MH, Stalpers LJ, Dijkgraaf MG et al.** Prophylactic vesical instillations with 0.2% chondroitin sulfate may reduce symptoms of acute radiation cystitis in patients undergoing radiotherapy for gynecological malignancies. *Int Urogynecol J* 2011; 226: 725–30

60 **Shao Y, Lu GL, Shen ZJ.** Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. *BJU Int* 2012; 109: 691–4

61 **Sommariva ML, Sandri SD, Ceriani V.** Efficacy of sodium hyaluronate in the management of chemical and radiation cystitis. *Minerva Urol Nefrol* 2010; 62: 145–50

62 **Delgado JM, Samper P, Garrido J.** Hyaluronic acid in the prevention of radiation-induced cystitis (Abstr.). *Proc Am Soc Clin Oncol* 2003; 22: 752

63 **Samper Ots PM, López Carrizosa C, Rodríguez A et al.** Vesical instillations of hyaluronic acid to reduce the acute vesical toxicity caused by high-dose brachytherapy do not affect the survival: a five-year follow-up study. *Clin Transl Oncol* 2009; 11: 828–34

64 **Levine LA, Jarrard DF.** Treatment of cyclophosphamide-induced hemorrhagic cystitis with intravesical carboprost tromethamine. *J Urol* 1993; 149: 719–23

65 **Lojanapiwat B, Sripralakrit S, Soonthornphan S, Wudhikarn S.** Intravesicle formalin instillation with a modified technique for controlling haemorrhage secondary to radiation cystitis. *Asian J Surg* 2002; 25: 232–5

66 **Dewan AK, Mohan GM, Ravi R.** Intravesical formalin for hemorrhagic cystitis following irradiation of cancer of the cervix. *Int J Gynaecol Obstet* 1993; 42: 131–5

67 **Vicente J, Rios G, Caffaratti J.** Intravesical formalin for the treatment of massive hemorrhagic cystitis: retrospective review of 25 cases. *Eur Urol* 1990; 18: 204–6

68 **Ho CC, Md Zainuddin Z.** Alum irrigation for the treatment of intractable haematuria. *Malays J Med Sci* 2009; 16: 66–8

69 **Nordling J, van Ophoven A.** Intravesical glycosaminoglycan replenishment with chondroitin sulphate in chronic forms of cystitis. A multi-national, multi-centre, prospective observational clinical trial. *Arzneimittelforschung* 2008; 58: 328–35

70 **Kallestrup EB, Jorgensen SS, Nordling J, Hald T.** Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product. *Scand J Urol Nephrol* 2005; 39: 143–7

71 **Morales A, Emerson L, Nickel JC.** Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. *Urology* 1997; 49 (Suppl.):111–3

72 **Diamantopoulos J, Kapsalis Z, Pliotas G et al.** Use of sodium hyaluronate solution in patients suffering from post-radiation cystitis. *ESTRO* 2004

73 **Gonzalez Patino E, Salvador Garrido N, Cascallar Caneda L et al.** Protective effect on the urinary bladder mucosa of intravesical hyaluronic acid in cervix cancer patients treated with pelvic radiotherapy, weekly

chemotherapy and high-dose rate brachytherapy. Presented at 2008 World Congress of Brachytherapy

74 **Mañas A, Glaría L, Peña C et al.** Prevention of urinary tract infections in palliative radiation for vertebral metastasis and spinal compression: a pilot study in 71 patients. *Int J Radiat Oncol Biol Phys* 2006; 64: 935–40

75 **Demir HA, Savaş Şen Z, Emir S, Tunç B.** Successful treatment of cyclophosphamide-induced haemorrhagic cystitis with intravesical prostaglandin E1 in a child with non-Hodgkin's lymphoma. *Scand J Urol Nephrol* 2011; 45: 281–4

76 **Miura M, Sasagawa I, Kubota Y, Iijima Y, Sawamura T, Nakada T.** Effective hyperbaric oxygenation with prostaglandin E1 for radiation cystitis and colitis after pelvic radiotherapy. *Int Urol Nephrol* 1996; 28: 643–7

77 **Yamamoto M, Hibi H, Ohmura M, Miyake K.** Successful treatment of hemorrhagic cystitis secondary to cyclophosphamide chemotherapy with intravesical instillation of prostaglandin F2 alpha. *Hinyokika Kiyo* 1994; 40: 833–5

78 **Hemal AK, Praveen BV, Sankaranarayanan A, Vaidyanathan S.** Control of persistent vesical bleeding due to radiation cystitis by intravesical application of 15 (S) 15-methyl prostaglandin F2-alpha. *Indian J Cancer* 1989; 26: 99–101

79 **Ostroff EB, Chenault OW Jr.** Alum irrigation for the control of massive bladder hemorrhage. *J Urol* 1982; 128: 929–30

80 **Efros MD, Ahmed T, Coombe N, Choudhury MS.** Urologic complications of high-dose chemotherapy and bone marrow transplantation. *Urology* 1994; 43: 355–60

81 **Arrizabalaga M, Extramiana J, Parra JL, Ramos C, Díaz González R, Leiva O.** Treatment of massive haematuria with aluminium salts. *Br J Urol* 1987; 60: 223–6

82 **Bogris SL, Johal NS, Hussein I, Duffy PG, Mushtaq I.** Is it safe to use aluminum in the treatment of pediatric hemorrhagic cystitis? A case discussion of aluminum intoxication and review of the literature. *J Pediatr Hematol Oncol* 2009; 31: 285–8

83 **Kanwar VS, Jenkins JJ 3rd, Mandrell BN, Furman WL.** Aluminum toxicity following intravesical alum irrigation for hemorrhagic cystitis. *Med Pediatr Oncol* 1996; 27: 64–7

84 **Seear MD, Dimmick JE, Rogers PC.** Acute aluminum toxicity after continuous intravesical alum irrigation for hemorrhagic cystitis. *Urology* 1990; 36: 353–4

85 **Nakada T, Nakada H, Yoshida Y et al.** Hyperbaric oxygen therapy for radiation cystitis in patients with prostate cancer: a long-term follow-up study. *Urol Int* 2012; 89: 208–14

86 **Oliai C, Fisher B, Jani A et al.** Hyperbaric oxygen therapy for radiation-induced cystitis and proctitis. *Int J Radiat Oncol Biol Phys* 2012; 84: 733–40

87 **Davis M, MacDonald H, Sames C, Nand K.** Severe cyclophosphamide-induced haemorrhagic cystitis treated with hyperbaric oxygen. *N Z Med J* 2011; 124: 48–54

88 **Ajith Kumar S, Prasanth P, Tripathi K, Ghosh P.** Hyperbaric oxygen-A new horizon in treating cyclophosphamide-induced hemorrhagic cystitis. *Indian J Urol* 2011; 27: 272–3

89 **Mohamad Al-Ali B, Trummer H, Shamloul R, Zigeuner R, Pummer K.** Is treatment of hemorrhagic radiation cystitis with hyperbaric oxygen effective? *Urol Int* 2010; 84: 467–70

90 **Heath JA, Mishra S, Mitchell S, Waters KD, Tiedemann K.** Estrogen as treatment of hemorrhagic cystitis in children and adolescents undergoing bone marrow transplantation. *Bone Marrow Transplant* 2006; 37: 523–6

91 **Ordemann R, Naumann R, Geissler G, Bornhauser M, Schuler U, Ehninger G.** Encouraging results in the treatment of haemorrhagic cystitis with estrogen – report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; 25: 981–5

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

93 **Neheman A, Nativ O, Moskovitz B, Melamed Y, Stein A.** Hyperbaric oxygen therapy for radiation-induced haemorrhagic cystitis. *BJU Int* 2005; 96: 107–9

94 **Chong KT, Hampson NB, Corman JM.** Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. *Urology* 2005; 65: 649–53

95 **Bevers RF, Bakker DJ, Kurth KH.** Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. *Lancet* 1995; 346: 803–5

96 **Bui QC, Lieber M, Withers HR, Corson K, van Rijnsoever M, Elsaleh H.** The efficacy of hyperbaric oxygen therapy in the treatment of radiation-induced late side effects. *Int J Radiat Oncol Biol Phys* 2004; 60: 871–8

97 **Corman JM, McClure D, Pritchett R, Kozlowski P, Hampson NB.** Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen. *J Urol* 2003; 169: 2200–2

98 **Kalayoğlu-Beşişik S, Abdul-Rahman IS, Erer B et al.** Outcome after hyperbaric oxygen treatment for cyclophosphamide-induced refractory hemorrhagic cystitis. *J Urol* 2003; 170: 922

99 **Jou YC, Lien FC, Cheng MC, Shen CH, Lin CT, Chen PC.** Hyperbaric oxygen therapy for cyclophosphamide-induced intractable refractory hemorrhagic cystitis in a systemic lupus erythematosus patient. *J Chin Med Assoc* 2008; 71: 218–20

100 **Kuroda I, Kuwata Y, Kakehi Y.** Hyperbaric oxygen therapy for Wegener's granulomatosis with cyclophosphamide-induced hemorrhagic cystitis. *Int J Urol* 2002; 9: 470–2

101 **Miller J, Burfield GD, Moretti KL.** Oral conjugated estrogen therapy for treatment of hemorrhagic cystitis. *J Urol* 1994; 151: 1348–50

102 **Liu YK, Harty JI, Steinbock GS, Holt HA Jr, Goldstein DH, Amin M.** Treatment of radiation or cyclophosphamide induced hemorrhagic cystitis using conjugated estrogen. *J Urol* 1990; 144: 41–3

103 **Duthie G, Whyte L, Chandran H, Lawson S, Velangi M, McCarthy L.** Introduction of sodium pentosan polysulfate and avoidance of urethral catheterisation: improved outcomes in children with haemorrhagic cystitis post stem cell transplant/chemotherapy. *J Pediatr Surg* 2012; 47: 375–9

104 **Toren PJ, Norman RW.** Cyclophosphamide induced hemorrhagic cystitis successfully treated with pentosanpolysulphate. *J Urol* 2005; 173: 103

105 **Hampson SJ, Woodhouse CR.** Sodium pentosanpolysulphate in the management of haemorrhagic cystitis: experience with 14 patients. *Eur Urol* 1994; 25: 40–2

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

107 **Geisler JP, Linnemeier GC, Manahan KJ.** Recombinant factor VIIa to treat late radiation-induced hemorrhagic cystitis: a case report. *J Reprod Med* 2008; 53: 360–2

108 **Connolly SS, D'Arcy FT, Corcoran MO.** Recombinant activated factor VII to control life-threatening haemorrhagic radiation cystitis. *Ir J Med Sci* 2010; 179: 431–3

109 **Demesmay K, Tissot E, Bulabois CE et al.** Factor XIII replacement in stem-cell transplant recipients with severe hemorrhagic cystitis: a report of four cases. *Transplantation* 2002; 74: 1190–2

110 **Pihusch M, Bacigalupo A, Szer J et al.** Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. *J Thromb Haemost* 2005; 3: 1935–44

111 **Singh I, Laungani GB.** Intravesical epsilon aminocaproic acid in management of intractable bladder haemorrhage. *Urology* 1992; 40: 227–9

112 **Wang CH, Fang CC, Chen NC et al.** Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a

systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2012; 172: 988–96

113 **Bonetta A, Di Pierro F.** Enteric-coated, highly standardized cranberry extract reduces risk of UTIs and urinary symptoms during radiotherapy for prostate carcinoma. *Cancer Manag Res* 2012; 4: 281–6

114 **Cowan CC, Hutchison C, Cole T et al.** A randomized double-blind placebo-controlled trial to determine the effect of cranberry juice on decreasing the incidence of urinary symptoms and urinary tract infections in patients undergoing radiotherapy for cancer of the bladder or cervix. *Clin Oncol (R Coll Radiol)* 2012; 24: e31–8

115 **Campbell G, Pickles T, D'Yachova Y.** A randomised trial of cranberry versus apple juice in the management of urinary symptoms during external beam radiation therapy for prostate cancer. *Clin Oncol (R Coll Radiol)* 2003; 15: 322–8

116 **Chuang YC, Kim DK, Chiang PH, Chancellor MB.** Bladder botulinum toxin A injection can benefit patients with radiation and chemical cystitis. *BJU Int* 2008; 102: 704–6

117 **Vela-Ojeda J, Tripp-Villanueva F, Sanchez-Cortés E et al.** Intravesical rhGM-CSF for the treatment of late onset hemorrhagic cystitis after bone marrow transplant. *Bone Marrow Transplant* 1999; 24: 1307–10

118 **Gweon P, Shanberg A.** Treatment of cyclophosphamide induced hemorrhagic cystitis with neodymium:YAG laser in pediatric patients. *J Urol* 1997; 157: 2301–2

119 **Ravi R.** Endoscopic neodymium:YAG laser treatment of radiation-induced hemorrhagic cystitis. *Lasers Surg Med* 1994; 14: 83–7

120 **Veerasarn V, Boonnuch W, Kakanaporn C.** A phase II study to evaluate WF10 in patients with late hemorrhagic radiation cystitis and proctitis. *Gynecol Oncol* 2006; 100: 179–84

121 **Pomer S, Karcher G, Simon W.** Cutaneous ureterostomy as last resort treatment of intractable haemorrhagic cystitis following radiation. *Br J Urol* 1983; 55: 392–4

122 **Pillay PK, Teh M, Chua EJ, Tan EC, Tung KH, Foo KT.** Haemorrhagic chronic radiation cystitis – following treatment of pelvic malignancies. *Ann Acad Med Singapore* 1984; 13: 634–8

123 **Giné E, Rovira M, Real I et al.** Successful treatment of severe hemorrhagic cystitis after hemopoietic cell transplantation by selective embolization of the vesical arteries. *Bone Marrow Transplant* 2003; 31: 923–5

124 **Palandri F, Bonifazi F, Rossi C et al.** Successful treatment of severe hemorrhagic cystitis with selective vesical artery embolization. *Bone Marrow Transplant* 2005; 35: 529–30

125 **Cho CL, Lai MH, So HS, Kwok KK, Chan JC, Velayudhan V.** Superselective embolisation of bilateral superior vesical arteries for management of haemorrhagic cystitis. *Hong Kong Med J* 2008; 14: 485–8

126 **Perez-Mendoza R, Martinez P, Solares M, Badillo M, Gallo M, Jiménez-Rios MA.** Management of post-radiotherapy hemorrhagic cystitis refractory to conventional treatment. *BMC Cancer* 2007; 7 (Suppl. 1): A44

127 **Harkensee C, Vasdev N, Gennery AR, Willetts IE, Taylor C.** Prevention and management of BK-virus associated haemorrhagic cystitis in children following haematopoietic stem cell transplantation – a systematic review and evidence-based guidance for clinical management. *Br J Haematol* 2008; 142: 717–31

128 **Ribeiro RA, Lima-Junior RCP, Leite CA et al.** Chemotherapy-induced hemorrhagic cystitis: pathogenesis, pharmacological approaches and new insights. *J Exp Integr Med* 2012; 2: 95–112

129 **ClinicalTrials.gov Identifier.** NCT01659723. Available at: http://clinicaltrials.gov/ct2/show/NCT01659723. Accessed September 2012

130 **Madersbacher H, van Ophoven A, van Kerrebroeck PE.** GAG layer replenishment therapy for chronic forms of cystitis with intravesical glycosaminoglycans – a review. *Neurourol Urodyn* 2012; 32: 9–18

131 **Yin Y, Liao B, Gao Q, Song T, Liu GJ, Wu H.** Interventions for preventing hemorrhagic cystitis in patients undergoing hematopoietic stem cell transplantation. *Cochrane Database Syst Rev* 2011; (8)CD009212

Correspondence: Heather Payne, University College London Hospitals, 250 Euston Road, London NW1 2PG, UK.

e-mail: heather_payne@blueyonder.co.uk

Abbreviations: BMT, bone marrow transplant; GAG, glycosaminoglycan; HBO, hyperbaric oxygen; HC, haemorrhagic cystitis; HSCT, haematopoietic stem cell transplant; LENT/SOM, Late Effects of Normal Tissue (Subjective, Objective, and Management elements); Mesna, 2-mercaptoethane sodium sulphonate; RT, radiation therapy/radiotherapy; RTOG, Radiation Therapy Oncology Group; VAS, visual analogue scale.

