Bone Marrow Transplantation (2003) 32, 925–931

www.nature.com/bmt

Incidence and treatment of hemorrhagic cystitis in children given hematopoietic stem cell transplantation: a survey from the Italian association of pediatric hematology oncology–bone marrow transplantation group

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Summary:

The purpose of this multicenter study was to assess the incidence and the treatment of hemorrhagic cystitis (HC) in 1218 pediatric patients, with a mean age of 10.8 years, who underwent hematopoietic stem cell transplantation (HSCT). In all, 44 patients (3.6%) developed HC a median 23 days after HSCT. The incidence of HC was higher in allogeneic than in autologous HSCT recipients ($P = 0.0001$). Of the 44 patients, 37 (84%) recovered from HC in a median 30 days (range 3–100); the other seven children died while still suffering from HC. Hyperbaric oxygen therapy (HOT) achieved significantly better results than prostaglandin therapy ($P = 0.02$) in the treatment of grade II–III HC. By multivariate analysis, age <96 months and allogeneic HSCT were significantly associated with the occurrence of HC: $P = 0.008$ and 0.013, respectively. After a median follow-up of 5.75 years, the 5-year survival of patients who did or did not develop HC was: 43 *vs* 52%, $P = 0.03$, respectively. This study indicates that age and type of HSCT are factors predisposing to HC in children given HSCT and demonstrates the promising role of HOT in a conservative approach to HC treatment.

Bone Marrow Transplantation (2003) **32,** 925–931. doi:10.1038/sj.bmt.1704252

Keywords: hemorrhagic cystitis; pediatric hematopoietic stem cell transplantation; hyperbaric oxygen therapy; prostaglandins; BK virus

Hemorrhagic cystitis (HC) is a cause of morbidity and extended hospitalization after hematopoietic stem cell transplantation (HSCT). Its incidence has been reported to range from 7 to 68%.[1–3] HC is manifested in two forms: early-onset HC, which usually appears within 48–72 h following chemotherapy, and late-onset HC, which occurs during the first 2–3 months after HSCT.[2,4]

The pathogenesis of HC has not been completely clarified.[5] Early-onset HC has been associated mainly with cyclophosphamide and busulfan administration. These drugs can damage the uroepithelium directly or through their metabolites.[5–8] Conversely, late-onset HC has been shown by several authors to be associated with virus reactivation in immunocompromised patients.[5,9–11]

Regarding HC prophylaxis and treatment, the main recommendations are based on supportive measures such as hyperhydration, forced diuresis and continuous bladder irrigation.[12–14] The efficacy of mesna (2-mercaptoethane-sulfonate)[15–17] and prostaglandins[18–21] is still debated. Some authors have recently reported encouraging results with the use of hyperbaric oxygen therapy (HOT) in the treatment of severe, radiation-induced HC,[22–25] suggesting a possible role for HOT in HC of other etiology, too.[25,26]

In this retrospective study, the incidence of HC and the results of its treatment were investigated at five major Italian pediatric centers performing HSCT, where HOT had been introduced for refractory or severe HC.

Patients and methods

Definition of HC

HC was defined according to the criteria proposed by Brugieres *et al*[2] as follows: grade I, gross hematuria and thrombocytopenia; grade II, gross hematuria and clots; grade III, gross hematuria, clots and urethral obstruction. In patients with intermittent symptoms, onset of HC was defined as the first day of HC symptoms. The worst clinical

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Received 23 February 2003; accepted 03 June 2003

presentation was considered as the highest grade of HC. Resolution of HC was considered as the clearance of gross hematuria lasting at least 7 days after discontinuing any treatment. According to the time of onset, HC was defined as early or late if it occurred within or beyond 48 h of completing the conditioning regimen.

Complications concurrent with HC were classified according to published criteria, as follows: infections,[27] CMV reactivation,[28] acute and chronic graft-versus-host disease (GVHD)[29] and veno-occlusive disease.[30]

Data on HSCT and HC

From June 1983 to September 1999, 1218 first-time HSCT (allogeneic 615, autologous 603) were performed at five Centers belonging to the Italian Association of Pediatric Hematology-Oncology/Bone Marrow Transplant Group (AIEOP-TMO). *In vitro* T-cell depletion was used in 21 of 615 allogeneic HSCT (3.4%), while *in vitro* purging (mainly with mafosfamide) or positive selection was performed in 189 of 603 autologous HSCT (31.3%). A TBI-conditioning regimen was used in 646 patients; all the remaining 572 patients received a cyclophosphamide-based conditioning regimen. Most patients who underwent an unrelated allogeneic HSCT (149/184, 81%) received *in vivo* rabbit antilymphocyte serum (107 patients) or Campath-1G (42 patients) for GVHD prophylaxis.

All patients were nursed in a single room or in a HEPA-filtered room and received standard measures for the prevention of infectious complications: that is, nonabsorbable antibiotics for gut decontamination, acyclovir to prevent HSV and VZV infections, fluconazole for antifungal prophylaxis,[31] and weekly administration until post-transplant day +60 of aspecific intravenous immunoglobulin. Neutrophil and platelet engraftment was defined as occurring on the first of three consecutive days on which the neutrophil and platelet counts exceeded 0.5×10^9/l and 50×10^9/l, respectively. Early post-HSCT toxicity was classified according to Bearman's criteria.[32] Table 1 shows the main clinical characteristics of the patients with and without HC.

Table 1 Clinical characteristics of patients with and without HC

	Group with HC (44 patients)	*Group without HC (1174 patients)*
Sex		
M	33 (75%)	690 (59%)
F	11 (25%)	484 (41%)
Age at transplant (years)		
Mean; (range)	10.8 (2.8–18)	8.1 (0.8–18)
Diagnosis		
Hematological malignancies	35 (79.5%)	698 (59.5%)
Solid tumors	2 (4.5%)	317 (27%)
Others (ie, inborn errors, aplastic anemia)	7 (16 %)	159 (13.5%)
Type of transplant		
Autologous	6 (14%)	597 (51%)
Allogeneic	38 (86%)	577 (49%)
Related	18 (47%)	413 (72%)
Unrelated	20 (53%)	164 (28%)
Source of stem cells		
Bone marrow	36 (82%)	907 (77%)
Peripheral blood	4 (9%)	226 (19%)
Cord blood	4 (9%)	41 (4%)
Conditioning regimen		
TBI	25 (57%)	621 (53%)
Cy + other	19 (43%)	553 (47%)
*GVHD prophylaxis**	(38 patients)	(577 patients)
CSA	10 (26%)	271(47%)
CSA + MTX + other	21 (55%)	191 (33%)
Other	7 (19%)	115 (20%)
TNC infused ($\times 10^8$/kg) mean (range)	2.69 (0.01–5.90)	3.64 (0.02–61)
Neutrophil engraftment (days), mean (range)	19.6 (8–54)	18.3 (3–94)
Platelet engraftment (days), mean (range)	52.1 (13–133)	44.8 (6–196)

*Allogeneic patients only; CSA = cyclosporin; MTX = short methotrexate; TNC = total number of nucleated cells.

Prevention and diagnosis of HC

In all patients, chemical HC prevention during the conditioning regimen was based on hyperhydration, at least 3000 ml/m^2/24 h of fluids being administered as a continuous infusion. Mesna was used in all patients who received cyclophosphamide in the conditioning chemotherapy and 12 of the 44 patients (27%) who developed HC had had a vesical catheter inserted during the conditioning regimen.

Routine urine analysis with microscopic examination or dipstick urine analysis at the bedside was performed twice daily during conditioning and was continued in the case of any genitourinary complications. All patients had a clinical evaluation and biochemical tests for renal and hepatic function, daily during the pre-engraftment period and then at least three times a week up to day +100, or longer, depending on the patient's clinical status. Weekly surveillance cultures for bacterial and fungal agents were obtained from urine during the aplastic phase and, in the event of hematuria, urine analysis included viral detection by culture (adenovirus), viral coat and antigenemia pp65 (cytomegalovirus) and, more recently, polymerase chain reaction (cytomegalovirus, polyomavirus BK and JC). Renal and pelvic ultrasound scans were performed to investigate any genitourinary abnormalities in patients with hematuria.

HC treatment

HC was managed with supportive care, prostaglandin and HOT. Prostaglandin and HOT were used at the physician's discretion for severe and/or refractory forms of HC.

Standard supportive measures included hyperhydration, forced diuresis, insertion of a vesical catheter for intermittent or continuous bladder irrigation and evacuation of clots. Irradiated leuko-depleted red blood cell transfusions

or single-donor platelet transfusions were used to maintain the hemoglobin level and platelet count above 8 g/l and 20×10^9/l, respectively.

Prostaglandin E2 (PGE2, Dinoprostone) was administered according to a previously described procedure.[33,34] Briefly, a vial containing 0.75 mg of PGE2 was diluted in 50–100 ml of normal saline and instilled slowly into the bladder through a two- or three-way urethral catheter. Then, the catheter was clamped and the solution was left *in situ* for 1–2 h. Before the procedure, all intravenous hydration was stopped and premedication with analgesics (morphine), sedatives (diazepam or analogues) and antispasmodics was given to relax the patient and prevent pain or discomfort due to bladder spasms. If the pain or the stimulus to void was intolerable, 25–50 ml of solution was drained from the bladder in order to achieve the desired dwelling time. The treatment was repeated daily until resolution of gross hematuria or for at least 1 week before considering the patient as a nonresponder.

Hyperbaric therapy

HOT was delivered by multiplace air-pressurized hyperbaric chambers, where oxygen was administered to the patients through oral-nasal masks. The masks were connected to a scuba regulator and to a discharge system that conveyed the exhaled air out of the chamber. The concentration of oxygen effectively inhaled by each patient exceeded 90% and was constantly monitored by an oximeter on an external control panel. To guarantee the maximum security during treatment, chamber pressure, humidity, oxygen concentration and temperature were monitored continuously and kept as follows: pressure at 2.5 bar, humidity above 50%, oxygen concentration below 23.5% and temperature between 22 and 26°C.

A single session of HOT consisted of three periods, lasting 25 min each, of breathing oxygen and two periods, lasting 5 min each, of breathing chamber air. At the beginning of the HOT session, the planned pressure was reached within 10 min, while, at the end of the third period, with the patient breathing through the oxygen mask, the chamber was slowly decompressed at the speed of 1 m per minute until reaching the atmospheric pressure.

Before the patient entered the chamber, Eustachian tube function was assessed and, if necessary, myringotomy was performed.

HOT was performed until gross hematuria disappeared or for a minimum of 1 week before considering the patient as a nonresponder.

Statistical analysis

Data were collected by each AIEOP BMT center adopting a web database created by Oracle and protected by Ianus® technology, implemented at the Inter-University Computing Center (CINECA). Data are stored in a central database (AIEOP BMT Registry), organized at the AIEOP Operations Office. Overall survival was estimated according to the Kaplan–Meier method. Comparisons between probabilities in different patient groups were performed using the Wilcoxon and log-rank tests. The observation time was censored as at the date of latest follow-up if no event (death due to any cause) was observed. Follow-up was updated as at December 31, 2001. Results are expressed as probabilities (%) and 95% confidence limits.

The influence of the following factors on the occurrence of HC was tested in univariate analysis: sex; underlying disease (hematological malignancy *vs* solid tumor *vs* others); age at HSCT; type of HSCT (allogeneic *vs* autologous HSCT); source of hematopoietic stem cells (bone marrow *vs* peripheral blood *vs* cord blood), use of TBI during the preparative regimen; type of GVHD prophylaxis (CSA *vs* CSA + MTX ± other *vs* other); total nucleated cells infused; time of neutrophil and platelet engraftment; acute GVHD occurrence. The influence of the above-mentioned factors in combination with other parameters, for example, platelet level and the use of prohemorrhagic drugs (heparin) at time of HC, on the severity of HC (grade I *vs* grade II–III) was also evaluated.

The χ^2 or Fisher exact tests were used for comparisons in the case of categorical variables, while the *t*-test was used for continuous variables. All *P*-values are two-sided and values <0.05 were considered statistically significant. Factors proving significant in univariate analysis were entered into a stepwise logistic regression model, in which the occurrence and severity of HC (grade II–III *vs* grade I) were considered as dependent variables. The SAS package (SAS Institute, Cary, NC, USA) was used to analyze the data.

Results

HC occurred in 44 of the 1218 patients analyzed (3.6%); 32 were males and 12 were females. HC was classified as early in five (11%) and late in 39 cases (89%). The median time of HC diagnosis was 23 days after HSCT, ranging between day −1 and day + 58. Most cases of HC (39/44, 88%) were diagnosed after 1995. HC lasted from 3 to 100 days, 30 days being the median duration. Allogeneic HSCT was associated with a significantly higher incidence of HC than autologous HSCT, that is, 38/615 cases (6%) *vs* 6/603 (1%) ($P = 0.0001$). HC scored as grade I in 11/44 cases (25%), grade II in 15/44 (34%) and grade III in 18/44 (41%).

The median platelet level at HC diagnosis was 30×10^9/l (range 4–213). Of the 44 patients, 19 (43%) were receiving anticoagulants (heparin in 15 cases, defibrotide in four) when HC occurred. These drugs were being used for veno-occlusive disease prophylaxis or treatment. Genitourinary ultrasound was performed in 24 of the 44 cases of HC (54%) and the main findings were as follows: thickening of bladder mucosa in 19/24 cases (79%) and clots in the bladder in 20/24 cases (83%).

Urine culture was negative for bacterial infection in 39 of the 44 cases (88%) tested. A potential viral etiology for one or more viruses was sought in 27 of 44 cases (61%) and the results were as follows: CMV positivity in five of 19 cases investigated; BK virus positivity in six of 17 cases investigated; no positivity for adenovirus or JC virus in 17 and two cases investigated, respectively.

Complications concurrent with the onset of HC are shown in Table 2, infections, CMV reactivation and acute GVHD being the most frequently reported.

Table 2 Type and incidence of HSCT complications concurrent with HC

Complication	*Type*	*Total (%)*
Infection	Fever of unknown origin	6
	Microbiologically defined infection: sepsis 3 1 *Escherichia coli* 1 *Pseudomonas* sp 1 *Streptococcus acidominimus* pneumonia 3 1 CMV 1 *respiratory syncitial virus*	6
	Clinically defined infection: sepsis 1 interstitial pneumonia 1 (etiology not determined)	2
		14/44 (32)
CMV reactivation		13/44 (29)
Veno-occlusive disease		3/44 (7)
Acute GVHD*	Grade 0–I, 12; Grade II–III, 26	38/44 (86)

*Allogeneic bone marrow patients only.

HC treatment

Patients were treated with hyperhydration (34/44, 77%) and/or bladder irrigation via two-way (29/44, 66%) or three-way (7/44, 16%) urethral catheter, and they required blood and platelet transfusions during HC. All but two treatments with PGE2 or HOT were performed after 1995. PGE2 treatment was administered to 19 of the 44 patients (43%), a median of 11 days after the onset of HC (range 0–69) and for a median 6 days (range 1–23). HC scores were I and II–III in four and 15 episodes, respectively. HOT was used in 14 of the 44 episodes of HC (32%), including five episodes previously treated with PGE2; moreover, the HC score was II–III in all patients treated with HOT. The median interval between the onset of HC and starting HOT was 26 days (range 6–79). The median duration of HOT was 17 days (range 4–58).

Neither PGE2 therapy nor HOT was ever withdrawn due to intolerability or severe complications. The comparison of the variables relating to the patient (sex, age at diagnosis, age at transplant), the disease (leukemia-lymphoma *vs* solid tumor) and the transplant (type, source of donor, conditioning regimen, engraftment for neutrophils and platelets) revealed no significant differences between the PGE2 and HOT groups (data not shown), but the success rate differed significantly, being 37% (7/19) for PGE2 and 78.5% (11/14) for HOT, $P = 0.002$.

Outcome of patients with HC

None of the patients required cystotomy or ureteronephrostomy for HC. Of the 44 patients, 37 (84%) recovered from HC in a median 30 days (range 3–100), while seven died while still suffering from HC. Overall, 25 of the 44 patients (57%) died a median 136 days after HSCT (range 19–721). The causes of death in these 25 patients were: infections, eight (32%), that is, interstitial pneumonia five, pulmonary mycosis two, sepsis by *Pseudomonas* sp one; disease progression, six (24%); GVHD, five (20%); multiple organ failure, two (8%); acute respiratory distress syndrome, three (12%); and thrombotic thrombocytopenic purpura, one (4%).

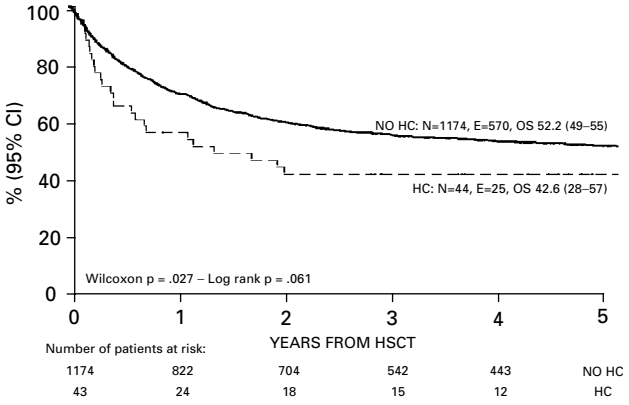

Figure 1 AIEOP BMT registry overall survival by HC. E = events; OS = overall survival

The overall 5-year survival of the 1218 patients analyzed was 52.2% (CI 49–55) after a median follow-up of 5.75 years (range 0.16–18.5). Figure 1 shows that the 5-year survival of patients with and without HC differed significantly: 43% (CI 30–56) *vs* 52% (CI 51–53), $P = 0.03$.

Prognostic factors for HC

Table 3 shows the factors associated with the development of HC in univariate analysis: underlying disease, $P = 0.004$; male sex, $P = 0.04$; age at HSCT, $P = 0.002$; allogeneic HSCT, $P = 0.0001$; type of donor, $P = 0.0001$; source of bone marrow, $P = 0.04$; type of GVHD prophylaxis, $P = 0.01$; acute II–IV GVHD, $P = 0.01$. By multivariate analysis, only age at HSCT ($<$ *vs* $\geqslant$96 months) and the type of HSCT (allogeneic *vs* autologous) remained statistically significant in the whole population, being $P = 0.008$, RR 0.29 and 0.013, RR 5.14, respectively. Among children given allogeneic HSCT, the following factors proved significant in multivariate analysis: age at HSCT ($<$ *vs* $\geqslant$96 months, $P = 0.016$, RR 0.24); sex (M *vs* F, $P = 0.026$, RR 3.15; and occurrence of GVHD (grade II–IV *vs* 0–I, $P = 0.043$, RR 2.71).

In univariate analysis, the severity of HC (score II–III *vs* score I) was significantly associated with sex, $P = 0.04$; underlying disease, $P = 0.03$; time to platelet engraftment, $P = 0.04$; and grade II–IV acute GVHD, $P = 0.05$. By multivariate analysis, male sex was the only factor significantly associated with the more severe form of HC, $P = 0.04$, RR 1.6.

Discussion

HC is a common cause of morbidity after HSCT and may give rise to serious complications, such as urinary obstruction, acute renal failure and hydronephrosis. The reported mortality of patients developing HC is 5%.[32,35] The incidence of HC varies in different reports.[2–4,9,10,36–38]

Table 3 Factors proving significantly associated with the development of HC in univariate analysis

	HC group	*No HC group*	*P-value*
Diagnosis			0.004
Leukemia/lymphoma	35	698	
Solid tumors	2	317	
Others	7	166	
Sex			
Male	33	690	0.04
Female	11	484	
Age at transplant, years mean (range)	10.8 (2.8–18)	8.1 (0.8–18)	0.002
HSCT			
Allogeneic	38	577	0.0001
Autologous	6	597	
Donor type			0.0001
Related	18	413	
Unrelated	20	164	
Autologous	6	597	
Stem cells source			0.04
Bone marrow	36	907	
Peripheral stem cells	4	226	
Cord blood	4	41	
TBI			
Yes	25	621	0.6
No (Cy + other)	19	553	
GVHD prophylaxis			0.01
CSA	10	271	
CSA + MTX ± other	21	191	
Other	7	115	
TNC infused ($\times 10^8$/kg) mean	2.69 (0.01–5.90)	3.64 (0.02–61)	0.009
Platelet engraftment, days, mean (range)	52.1 (13–33)	44.8 (6–196)	0.2
Neutrophil engraftment, days, mean (range)	19.6 (8–54)	18.3 (3–94)	0.4
Acute GVHD			
Grade II–IV *vs* 0–II	26	232	0.001
	12	345	

CSA = cyclosporin; MTX = short methotrexate; TNC = total number of nucleated cells; TBI = total body irradiation; GVHD = graft-versus-host disease.

Factors such as age and the type of HSCT (autologous or allogeneic), and the criteria used to define HC may explain the differences to some degree at least.

By contrast with the report from Bedi *et al*,[38] our data showed a higher incidence of HC in allogeneic HSCT recipients than in children given an autologous transplant. In logistic regression analysis, predictive factors associated with the development of HC were younger age, allogeneic HSCT and GVHD. These findings are consistent with several reports demonstrating a prognostic role for GVHD alone[39,40] or in combination with other factors, for example, the use of busulfan or cyclophosphamide in the conditioning regimen, a mismatched donor and age.[4,35] Moreover, the lower survival we found in patients with HC is consistent with the Nevo *et al*[36] report, where bleeding in GVHD clearly identified a poor-outcome subgroup.

Although HC etiology and pathogenesis are still not fully understood, attributing HC to a direct effect of toxic metabolites on the bladder mucosa is insufficient. It has recently been suggested that HC is a symptom of the reactivation of an urotropic viral infection, occurring during deep and prolonged immunosuppression. This hypothesis is supported by the observation of an association between HC and both allogeneic HSCT and GVHD.[35,39] In this case, the pathogenesis of HC would be comparable to the immunopathological model of CMV reactivation or CMV disease.[40,42]

Several authors[5,9–11,36–41] have associated adenovirus (and subtype 11 in particular) and polyomavirus (BK) with HC. The role of these viruses in the pathogenesis of HC has been suggested by the strong temporal correlation between the onset of viruria and HC[38,42] and the relationship between HC and high virus levels in the urine, as determined by quantitative PCR.[11,43] We found an association between PCR-determined BK viruria and HC in 35% of the cases investigated. Confirmation of the role of viral reactivation in inducing HC may prompt the use of antiviral drugs in the management of HC. In this context, an *in vitro* activity and clinical efficacy have been anecdotally reported for ribavirin,[44–47] for vidarabine[48–50] and, more recently, for cidofovir.[51–53]

Although most cases of HC can be managed with a conservative approach, bladder tamponade or refractory HC may require surgical treatment, such as cystotomy or cystectomy with urinary diversion,[54,55] particularly in children (where the smaller urethra precludes the use of large catheters for clot removal). Cystoscopy may be useful for this purpose and to cauterize the mucosa, provided bleeding is not diffuse.

To preserve the bladder, several compounds (eg alum, phenol, silver nitrate, formalin and prostaglandins) have been tried in intravesical instillation: prostaglandins are potentially the most advantageous because of their multiple effects on vascular epithelium (vasoconstriction, platelet aggregation) and bladder function (cytoprotection, barrier against infection and ulceration, smooth muscle contraction), and their relatively low toxicity and good tolerability profile. Few data are available on their use, but the reported efficacy ranges from 50 to 100%.[33,34,56] Our findings showed a limited efficacy of prostaglandins, however, especially in more severe HC, where the success rate was significantly lower than with HOT. In this study, prostaglandins were introduced a median 11 days after the onset of HC and it may be that their prompter use, within 48 h of the onset of HC, could improve their efficacy, although to date no reports have documented the timing of starting prostaglandin therapy as a key point for its efficacy.

The main finding emerging from our data was the superiority of HOT over the other measures used to treat HC, although it was used in the most severe cases and introduced late, when supportive measures and PGE2 had already failed to control the disease.

HOT is extensively used where tissue damage is caused by hypoxic injury, for its capacity to stimulate angiogenesis and prompt healing.[57] Radiation-induced and chemical HC are characterized by much the same mucosal damage, for example, progressive obliterative endoarteritis of small vessels, telangiectasia, ischemia, ulceration, bleeding and eventually fibrosis. The efficacy of HOT in HC induced by pelvic irradiation has already been reported by several authors,[22–25] but only anecdotal reports have analyzed the role of HOT in HC after HSCT.[25,58] The high cure rate (78.5%) obtained in our study, in patients refractory to other medical treatments, suggests that HOT may play an important part in a conservative approach to HC in HSCT recipients too. Other potential advantages, such as a faster recovery from HC, the need for fewer transfusions and a shorter hospital stay should be addressed by future controlled trials.

In conclusion, this study confirms that HC is a relatively common complication, particularly after allogeneic HSCT, and that HOT can successfully cure the most severe forms of HC and offer an advantage in terms of prognosis and potential sequelae.

Acknowledgements

The authors thank Lucia Agostini, PhD, and Sandra Volpato, PhD for their help in the data analysis, Judith Kingston, MD, for reviewing the English style of the manuscript, and the nursing staff at each centre caring for the patients.

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