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Intravesical application of platelet-rich plasma in patients with persistent haemorrhagic cystitis after hematopoietic stem cell transplantation: a single-centre preliminary experience

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Abstract

Purpose Haemorrhagic cystitis (HC) after allogeneic transplantation (HSCT) is a condition characterized by diffuse inflammation and bleeding from the bladder mucosa. Treatment of HC is not standardized and clinical Guidelines are elusive. The aim of this study was to evaluate the safety and efficacy of intravesical treatment with platelet-rich plasma (PRP) in patients with HC after allogenic HSCT.

Methods Data from ten consecutive patients with BK virus-induced HC between 2013 and 2017 were collected. HC was classified into four grades. Inclusion criteria were (a) grade 3 or 4 BKV-induced HC after allogenic HSCT; (b) HC refractory to conservative therapy. All patients underwent transurethral cystoscopy and PRP treatment under general anaesthesia.

Results Mean patients' age was 33.6 years. Four patients (40%) presented a grade 3 BKV-induced HC and six patients (60%) a grade 4. No intraoperative complications occurred. Postoperative complications were recorded in six patients: three patients required blood transfusion while three patients endovenous antibiotic therapy. Median time to catheter removal was 6 days (IQR 2–10). Median length of hospitalization was 35 days (IQR 6–73). At 30 days after surgery, a three-way catheter was repositioned in one patient for grade 4 haematuria, six patients had a complete response, and three a partial response.

Conclusions Our preliminary experience suggests that intravesical administration of PRP should be considered as a feasible and safe option for the treatment of BK-induced HC after HSCT. Future studies are needed to assess its potential value in other forms of haemorrhagic cystitis.

Keywords Allogeneic hematopoietic transplantation · Bladder irrigation · Haematuria · Hemorrhagic cystitis · Platelet-rich plasma

Introduction

Haemorrhagic cystitis (HC) is a clinical condition characterized by a diffuse inflammation of the bladder mucosa determining irritative voiding symptoms and urinary bleeding, ranging from a transient situation to a life-threatening intractable hematuria [1, 2]. In most cases, the full understanding of underlying disease, including interstitial cystitis (IC), bladder pain syndrome (BPS), viral infection, chemotherapeutic- and radiation-induced HC, is often delayed with consequent potential disease progression [3]. The HC may also occur after a hematopoietic stem cell transplantation (HSCT), as a major complication reported approximately in 0–10% of the cases [4]. In these cases, HC develops in the first days after HSCT if related to the exposure to the oxazaphosphorines (i.e. cyclophosphamide and ifosfamide), while in a minority of cases it has typically a late onset and it is caused by the immunodepression and the consequent infection by ubiquitous viruses such as BK and adenovirus [5, 6]. In this clinical setting, HC significantly affects the

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quality of life, prolonging hospitalization and increasing the cost of allogeneic HSCT [7].

The treatment options for HC after HSCT are not standardized, and the available clinical guidelines are elusive to this regard [8]. The catheter placement with continuous bladder irrigation has often only a supportive intent. The administration of antiviral therapy, fluoroquinolones or the use of hyperbaric oxygen therapy has been reported as medical measures with no clear effectiveness [9]. Surgical management may include fulguration, vesical artery embolism, and even partial or total cystectomy [10, 11]. Other authors proposed the endoscopic application of fibrin glue on the bleeding bladder mucosa to reduce the haematuria and the voiding symptoms [12, 13].

Platelet-rich plasma (PRP), also termed autologous platelet gel, plasma rich in growth factors (PRGF), platelet concentrate (PC), is essentially an increased concentration of autologous platelets suspended in a small amount of plasma after centrifugation [14].

Platelets play a fundamental role in haemostasis and are a natural source of growth factors. Growth factors, stored within platelet α-granules, include platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), platelet-derived angiogenic factor (PDAF), and transforming growth factor beta (TGF-β).

The potential beneficial role of PRP on the therapeutic angiogenesis and tissue formation could be applicable in several clinical fields, including arthroscopic rotator cuff repair, in regenerative endodontic treatment, and in reducing alveolar bone resorption following rapid maxillary expansion [15–17]. Moreover, PRP also gives advantages in the management of skin wounds [18].

Despite the exponential increase of HSCT in the last decade, the HC remains an unsolved complication without any standardized treatment. Moreover, the late decision-making progress often determines a reduction of the effectiveness of the treatment procedures.

The aim of this study was to evaluate the potential benefits of intravesical application of PRP in patients with BK virus-induced HC after HSCT, analysing the clinical outcomes in a tertiary referral Italian centre for HSCT.

Methods

Study population

In accordance with ethics committee approval, we included and retrospectively evaluated the clinical data of patients treated with PRP for HC after a HSCT between January 2013 and September 2017.

Baseline characteristics, including age, body max index (BMI) and the Charlson Comorbidity Index (CCI) and previous eventual treatments for HC were collected. Preoperative and postoperative hematologic assessments, including preoperative platelet count, haemoglobin and haematocrit as well as coagulative evaluation (INR, PT, PTT, fibrinogen) were recorded. All patients performed before the HSCT a serological screening for infectious diseases including immunodeficiency virus (HIV), hepatitis B (HBV), hepatitis C virus (HCV) and cytomegalovirus (CMV).

Thiotepa-based conditioning regimen for HSCT was administrated in all cases. All patients were treated with antiviral therapy for 15 days: one using Cidofovir, four using Valganciclovir + Cidofovir, and five using Cidofovir + Foscarnet.

HC was classified into four grades: microscopic haematuria (grade 1), macroscopic haematuria (grade 2), haematuria with clots requiring transfusion support (grade 3), and macroscopic haematuria with clots and impaired renal function (grade 4) [19]. BK viruria was verified in all patients before transplantation and periodically after discharge and at 1-month follow-up visit. A positive result was considered significant for values $> 9 \times 10^6$ copies/ml.

In this study, were included only patients with (1) grade 3 or 4 HC, (2) BK virus-induced disease after HSCT diagnosed through a polymerase chain reaction (PCR) in both urine and plasma without previous treatments for HC, and (3) treated with the endoscopic PRP application in the bladder.

Platelet-rich plasma preparation

The PRP is a leukocyte-free autologous plasma prepared from the patient's own blood or from the homologous compound. It contains the plasma proteins, such as fibrin, fibronectin, and vitronectin, and factors produced by platelets, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), insulin-like growth factor (IGF) and epidermal growth factor (EGF). The rationale is to create a homologous compound able to initiate haemostasis as well as contribute to wound healing and tissue repair and adhesion of fibroblasts.

PRP is generally prepared centrifuging one unit of homologous platelet apheresis (250 cc) in a sterile fashion first at 200 g for 20 min, then at 2000 g for other 20 min using a constant temperature of 24 °C. The product of centrifugation is approximately 50 mL of sterile PRP. Afterwards, 10 ml of plasma are subsequently added and the product is preserved at 4 °C. About 30 min before use 10 ml of 10%-calcium gluconate was added (platelet activator) (Fig. 1).

Fig. 1 On the left, the product of centrifugation of sterile PRP; on the right, the platelet activator (10%-calcium gluconate)

Intervention technique

The patients undergo general anaesthesia and are placed in supine gynaecological position with a 10° Trendelenburg. Patients are submitted to a single-shot preoperative antibiotic prophylaxis (generally 2 g cefazoline). Cystoscopy is performed with Iglesias resectoscope 26 Ch Storz using a 1.5% glycine irrigation. During the cystoscopy the bladder is irrigated, the major clots are removed and a fulguration of the major bleeding areas is performed. Afterwards, an intravesical pressure of 15 mmHg of CO_2 is created for 15 min using a laparoscopic insufflator. Then 50 mL of PRP are instilled and equally distributed on the bladder mucosa using a 5-Fr sterile ureteral catheter. The solution is maintained for 15 min in the bladder. The previous distension with carbon dioxide is performed to achieve a homogeneous distension of the bladder and to facilitate the contact of PRP with the vesical mucosa. Afterwards, a 20 CH double-way urethral catheter is inserted.

Definition of outcomes

The postoperative haemoglobin was assessed at the first and third postoperative (POD) day, at discharge and at 1 month from the procedure. The number of blood transfusions required including red cells, platelets and apheresis were collected. The intraoperative and postoperative complications were assessed and valued according to the Clavien–Dindo classification [20]. Frequency and dysuria were evaluated using Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF Scale). This questionnaire comprises eight questions, investigating symptoms (urgency, pain) and bother domains. Patients who achieved a total score between 0 and 4 resulted negative for symptoms due to HC. When the total score was between 5 and 9, patients had 57% of likelihood to had storage symptoms; if it is between 10 and 14 or between 15 and 19 the probability rises to 75% and 79%, respectively. If the score exceeds 20 points, the percentage of storage symptoms is very high (93%) [21].

The time to catheter removal, the length of hospitalization and the readmission rate with need of urethral catheterization for haematuria were assessed.

The patients were followed up in the outpatient department at 1 month from the procedure.

A complete response to PRP treatment was defined as (a) the disappearance of dysuria, urgency, and frequency; (b) the catheter removal without persistence of haematuria; (c) no readmission for haematuria. A partial response was defined if the first two outcomes were achieved, but the patient experienced a readmission. A persistent HC was defined if the clinical signs and symptoms continued after the treatment.

Results

Overall, 59 patients developed HC during hospitalization, after allogenic HSCT. Of these, 10 (16.9%) patients fulfilled the inclusion criteria and were included in the analytic cohort.

Patients had a median age of 33.6 ± 7.2 years (IQR 18–53). The median CCI at baseline was 3 (IQR 2–5); the median BMI was 21.5 (IQR 18.6–26.3). The haematological pathology leading to HSCT was myelodysplasia in 2 patients (20%), myeloid chronic leukaemia in one patient (10%), myeloid acute leukaemia in three (30%), polycythaemia vera in one (10%) and B cells lymphoblastic leukaemia in three (30%). Overall, four patients (40%) presented a grade 3 BKV-induced HC and six patients (60%) had a grade 4 BKV-induced HC.

The pre- and postoperative hematologic and coagulative assessments are shown in Table 1. Preoperative screening for serological infections was negative in all the patients.

No intraoperative complication was recorded and the continuous bladder irrigation was performed only in one case postoperatively for 48 h. Postoperative Clavien–Dindo complications grade II were recorded in six (60%) patients: three (30%) patients required red cell and platelet transfusion while three patients were administered with endovenous antibiotic therapy. Median time to catheter removal was 6 days (IQR 2–10). Median length of hospitalization was 35 days (IQR 6–73). Median preoperative PUF total score was 15 (IQR 9–19). At 1-month follow-up visit, median postoperative PUF total score resulted to be 9 (IQR 4–11).

Only one (10%) patient was readmitted for massive haematuria at the 27th day after the intervention and a three-way catheter with continuous bladder irrigation was repositioned. At 1-month follow-up, six (60%) patients had a complete

Table 1 Hematologic and coagulative assessment of ten patients treated with the application of platelet-rich plasma (PRP) for the BK virus-induced HC after HSCT at baseline, and at 1st and 3rd POD, at discharge and at last follow-up

Hematologic parameters	Baseline	POD1	POD3	Discharge	Follow-up
Hb (g/dL)	8.8 ± 2.2	9.1 ± 1.0	9.3 ± 0.2	9.8 ± 1.2	10.5 ± 0.8
HCT (%)	28.3 ± 8.2	29.1 ± 8.0	30.3 ± 8.0	30.8 ± 7.5	30.9 ± 7.5
PLT ($\times 10^3$)	69.1 ± 112.9	69.4 ± 110.1	70.1 ± 105.5	71.2 ± 110.2	75.3 ± 104.5
INR	1.1 ± 0.2	1.1 ± 0.1	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.2
PT	72.0 ± 28	73.0 ± 25	73.0 ± 22	79.0 ± 20	83.0 ± 22
PTT	27.2 ± 4.0	27.9 ± 4.0	28.2 ± 3.0	30.2 ± 3.5	32.2 ± 4.5
Fibrinogen	370 ± 64	385 ± 63	380 ± 50	390 ± 55	384 ± 67

Hb haemoglobin, *HCT* haematocrit, *PLT* platelets, *INR* International Normalized Ratio, *PT* prothrombin time, *PTT* partial thromboplastin time

response, three (30%) had a partial response and one (10%) had no response to treatment, requiring hospital readmission.

Discussion

HC is a severe complication after HSCT and it can be often difficult to manage determining a deterioration of the patients' conditions, a delaying in patient discharge with a significant increase of costs. In the worst case scenario, HC after HSCT can also have a fatal outcome. The last decade has been characterized by an exponential increase of allogeneic and autologous transplantations with an extension of the indications toward solid tumours, autoimmune diseases and storage disorders [22]. Although this condition is extremely delicate for the frailty of these patients due to the therapy-induced immunosuppression, the interest of the urological community on this topic is still very low and the current international guidelines did not provide a general consensus for the endoscopic or surgical management of this condition.

In this study, we proposed a novel endoscopic technique for the management of BK virus-induced HC after HSCT. Indeed, the application of a PRP compound on the bladder mucosa after an electrocoagulation of the bleeding areas seems to determine an induction of haemostasis together with a wound healing and tissue repair and adhesion of fibroblasts.

No patient reported intraoperative complications. Overall, 60% and 30% of the patients reported a complete and partial response to the treatment, respectively. Moreover, the mean length of hospitalization was more than 1 month. This did not occur for urological procedure failure, rather than to patients' general clinical conditions related to the disease itself. Indeed, the mean time of catheter removal was less than 1 week.

A recent literature review investigated the role of different therapies in the management of severe HC in HSCT [9]. Most of these studies were retrospective and referred to a plethora of different therapies with no well-defined response criteria. The inflammatory response promoted by the ubiquitous virus infection seems to be the most important factor for the late onset of HC after HSCT. Several studies proposed the administration of intravenous cidofovir for the remission of virus-induced HC in immunosuppressed patients with a remission rate ranging between 60% and 84% [23–25]. However, most of the studies present relevant selection biases related to the characteristics of the study population, to the study design, to the quality of reporting and to the lack of well-defined criteria for clinical and viral response. Also the fluoroquinolone antibiotics have been shown an in vitro activity against BK virus; however, it was not possible to demonstrate a demonstrable reduction in HC incidence or severity. The preventive administration of 2-mercaptoethane sodium (MESNA) as uroprotective antitoxic agent has been studied in context of pre-engraftment HC. However, results are equivocal and only one trial reporting an advantage of MESNA over forced diuresis/hyperhydration. Hyperbaric oxygen therapy acts through an increased oxygen pressure in tissues increasing the neovascularisation of the tissues, the healing effect on injured tissues. This treatment showed interesting results in a multicentre Italian cohort of paediatric patients with post-engraftment HC [26]. Endoscopic fulguration, vesical artery embolism, standard open partial or even total cystectomy are used as last expedient when the haematuria becomes persistent and refractory to conservative measures [10, 11]. A recent study investigates the clinical effect and safety of surgical treatment for severe, refractory haemorrhagic cystitis (HC) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) with fulguration and selective embolization [27]. The authors evaluated patients with severe HC, who were refractory to medical managements and received bladder surgery including mucous electrocoagulation and/or selective transcatheter arterial embolization. Five patients did not respond to these methods, suggesting that alternative treatments are required.

Recently, the application of fibrin glue on the bleeding bladder mucosa through an endoscopic spray applicator has been proposed as an alternative treatment for HC [12]. Its application seemed to significantly reduce the bleeding and the voiding symptoms irrespective of the aetiology of the haematuria. Nevertheless, the authors were not able to demonstrate an improvement of the overall survival in these patients. Indeed, the fibrin sealant is biocompatible and biodegradable and proved to be effective for several other urologic diseases [25]. However, the limited availability and the high cost of this material may theoretically limit its widespread use. In this study, we tested a different sealant, which is competitive, non-invasive, economical and non-allergenic. PRP is proved to be efficacious in initiating wound healing and tissue repair and contributing to haemostasis and adhesion in other settings. The rationale of using PRP is to accelerate vascularization, improving tissue healing and enhance cell regeneration. Platelets and growth factors are involved in key stages, including chemotaxis, proliferation, differentiation, and angiogenesis [28]. Its potential benefits could be shown in several clinical fields, including arthroscopic rotator cuff repair, regenerative endodontic treatment, and alveolar bone resorption following rapid maxillary expansion [15–17]. Moreover, PRP also gives advantages in the management of skin wounds [18]. The intravesical instillation of PRP was first tested in rabbit models of interstitial and haemorrhagic cystitis and it was observed a regeneration of the bladder urothelium while decreasing the macroscopic bleeding [29]. Further studies reported that the intravesical PRP injections can be safely performed in human patients with interstitial cystitis or painful bladder syndrome [30]. This treatment determined a significant reduction of the symptoms reported by the patients [30].

In our preliminary experience, the intravesical application of PRP represents a safe and feasible technique, achieving optimal postoperative outcomes. Although the perioperative pain related to HC was not assessed with validated scores, all the patients reported a pain relief after the PRP application together with a disappearance of dysuria, urgency and frequency, according to validated questionnaire. All patients had a discontinuation of the analgesic treatments during the 24 h after the procedure. This treatment has potential applications for HC related to pelvic radiation treatment and other virus infections in immunosuppressed patients. On the other hand, it is difficult to expect a successful outcome of the PRP application also for the management of HC in other clinical settings, such as benign prostatic hypertrophy, prostate cancer or bladder cancer, as the pathophysiological mechanisms responsible of the haematuria have a different background. On these promises, the utilization of PRP could be extended to different categories of patients. Indeed, further studies are needed to evaluate also the postoperative outcomes on a higher number of patients and its impact on the overall survival in particular in immunosuppressed patients and to evaluate the role of PRP compared with other treatments.

This study is not devoid of limitations. The sample size of the population is low, and the patients were followed up only in the first postoperative month. However, the patients were highly selected and only those who had a verified BK virus-induced disease were included. On the other hand, these results are proven on a specific subgroup of patients and, therefore, are not generalizable to HC caused by different diseases. Another limitation is the lack of a control arm in this study. This is because we have experience with patients suffering from HC undergoing fulguration as the only treatment of choice: in this group, we found few benefits and high complication rate mainly in terms of readmission. Moreover, since the group of patient suffering from HC-BK virus induced is very much reduced, we preferred to treat all patients with PRP to provide a comprehensive preliminary report. Moreover, other concomitant treatments could have partly influenced the final outcomes. Acknowledged these limitations, this is the first, albeit preliminary, experience with PRP intravesical treatment of late HC after HSCT providing promising data on its efficacy and safety in a real-clinical practice.

Our preliminary experience suggests that intravesical administration of PRP should be considered as a feasible, safe, non-invasive and reproducible option for the treatment of BK-induced late-onset HC after HSCT. In particular, future series should standardize both technical aspects of PRP injection, including dose, modality of preparation and timing of administration, as well as the maximum number of deliverable cycles. Moreover, future prospective controlled studies are needed to assess its potential value also in other forms of HC and to provide evidence on the potential clinical impact of PRP intravesical therapy for HR in different clinical settings.

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Compliance with ethical standards

Conflict of interest The authors deny any potential conflicts of interest. All authors have no direct or indirect commercial financial incentive or interest associated with publishing the article.

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