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Fibrin Glue Therapy for Severe Hemorrhagic Cystitis after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Hemorrhagic cystitis (HC) occurring after allogeneic transplantation significantly affects quality of life and, in some cases, becomes intractable, increasing the risk of death. To date, its therapy is not established. We used the hemostatic agent fibrin glue (FG) to treat 35 patients with refractory post-transplantation HC. Of 322 adult patients undergoing an allogeneic transplantation for hematological malignancy, 35 developed grade $\geq$ 2 HC refractory to conventional therapy and were treated with FG, diffusely sprayed on bleeding mucosa by an endoscopic applicator. The cumulative incidence of pain discontinuation and complete remission, defined as regression of all symptoms and absence of hematuria, was 100% at 7 days and 83% $\pm$ 7%, respectively, at 50 days from FG application. The 6-month probability of overall survival for all 35 patients and for the 29 in complete remission was 49% $\pm$ 8% and 59% $\pm$ 9%, respectively. In the matched-pair analysis, the 5-year probability of overall survival for the 35 patients with HC and treated with FG was not statistically different from that of the comparative cohort of 35 patients who did not develop HC (32% $\pm$ 9% versus 37% $\pm$ 11%, P = not significant). FG therapy is a feasible, effective, repeatable, and affordable procedure for treating grade $\geq$2 HC after allogeneic transplantation.

INTRODUCTION

Hemorrhagic cystitis (HC) is a major complication of allogeneic hematopoietic stem cell transplantation (HSCT), characterized by the presence of continuous macroscopic hematuria occurring in absence of gynecologic and urologic disease or bacterial and fungal infections of the urinary tract [1-5]. With symptoms ranging from hematuria to renal failure, HC significantly affects the quality of life, prolongs hospitalization, increases the cost of allogeneic HSCT [6], and, in some cases, can become an intractable and life-threatening disease [1-4]. Indeed, HC is correlated with an increased risk of transplantation mortality [7] and reduced probability of survival [8].

Discrepancies in defining the diagnostic criteria are partially responsible for the variability of HC incidence, which ranges from 7% to 68% in the setting of allogeneic HSCT [9,10]. HC occurring more than 10 days after transplantation is defined as late clinical form, ranges from 12% to 25%, and usually lasts from weeks to months [11]. A number of variables have been identified as significant risk factors for developing HC, including allogeneic HSCT, intensity of the conditioning regimen, alternative donor of hematopoietic stem cells (HSC) (haploidentical, matched unrelated donor, umbilical cord blood), and advanced grade of acute graft-versus-host disease (GVHD) [1-5,7]. Finally, reactivation of polyoma BK virus (BKV), adenovirus, and cytomegalovirus have been significantly correlated with higher incidence of

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clinical grade ≥2 HC [1-5,7]. In particular, the relationship between BKV reactivation and occurrence of late-onset HC remains an issue of discussion [12-14]. HC refractory to conventional therapies (hyperhydration, bladder irrigation, antiviral drugs, and transfusion support) is extremely difficult to manage and, to date, neither intravesical nor systemic therapy have been established [5,7,15-30]. Favorable results have been reported in some cases, but the experiences are limited and related to the expertise of a single transplantation center. Furthermore, most of these therapies are very expensive and sometimes complicated by relevant side effects, such as bladder fibrosis, urinary incontinence, or renal or nervous toxicity. Invasive and particularly aggressive approaches, such as fulguration, vesical artery embolism, nephrotomy, uretheral resection, and partial or total cystectomy have been variably proposed as ultimate therapeutic options in extremely debilitated patients with intractable and life-threatening forms of HC [31].

We report the results of treatment of grade 2 to 4 HC by using the human plasma-derived hemostatic agent fibrin glue (FG) through endoscopic application on bladder mucosa in adult patients submitted to allogeneic HSCT.

PATIENTS AND METHODS

HC Grading

HC was classified according to standard published criteria into 4 grades: microscopic hematuria (grade 1), macroscopic hematuria (grade 2), hematuria with clots requiring transfusion support (grade 3), and macroscopic hematuria with clots and impaired renal function (grade 4) [2,3].

Patient Selection Criteria

All patients with HC were first treated with conventional therapy consisting of hyperhydration, continuous bladder irrigation, transfusion support with platelet concentrates, and, limited to 15 patients, cidofovir. Patients selected for FG treatment met the following criteria: (1) progression from grade 1 to grade ≥2 HC on conventional therapy, and (2) grade ≥ 2 HC not responding to conventional therapy.

Patients

Between January 2006 and December 2012, 1137 patients (children, n = 246; adults, n = 891) underwent HSCT for malignant and nonmalignant diseases and were registered at the Rome Transplant Network, a Joint Accreditation Committee ISCT EBMT (JACIE)-accredited metropolitan transplantation program established in Rome and including 7 transplantation centers. Of 891 adult patients, 569 (64%) underwent autologous and 322 (36%) underwent allogeneic HSCT. No recipients of autologous HSCT experienced HC, which occurred in 76 (24%) patients submitted to allogeneic HSCT and was of grade ≥ 2 in 45 (14%). For the 322 allogeneic transplantations, the HSC source was HLA-identical sibling in 146, matched unrelated donor in 72, umbilical cord blood in 30, and haploidentical family donor in 74, with an incidence of grade ≥2 HC of 6%, 14%, 17%, and 28%, respectively. Of the 45 patients with grade ≥2 HC, 35 (78%) with median age of 35 years (range, 18 to 54) underwent endoscopic FG therapy, which was not feasible for the other 10 patients because of very severe clinical conditions with or without disease progression (Figure 1). The study was approved by the institutional review board of each participating institution. Informed consent for the treatment was obtained from all patients in accordance with the Declaration of Helsinki.

Patient and clinical characteristics of the 35 patients with grade ≥ 2 HC are summarized in Table 1.

Preventive Measures

Antithymocyte globulin was included in the conditioning regimen for all patients who underwent transplantation from an alternative donor. As antiinfective prophylaxis, all patients treated in high-efficiency particulate-filtered air rooms with positive pressure received ciprofloxacin combined with fluconazole and acyclovir. Hyperhydration, forced diuresis, and urine alkalinization were given to all patients during the conditioning regimen. As preventive measures for drug-related chemical cystitis, mercaptoethane sodium sulfonate was administered to patients receiving cyclophosphamide.

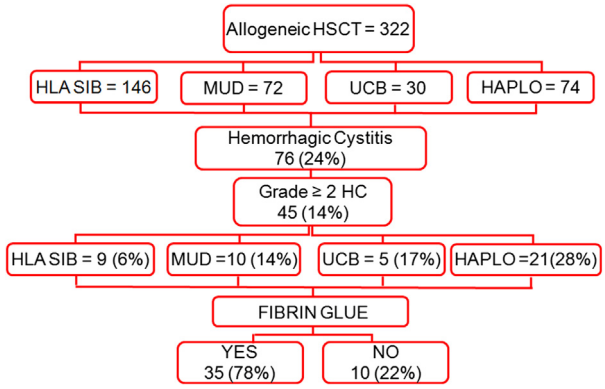

Figure 1. Epidemiology of hemorrhagic cystitis (Rome Transplant Network, January 2006 to December 2012).

Engraftment and GVHD Definition

Engraftment was defined as the first of 3 consecutive days of ≥.5 × 10^6/mL polymorphonuclear cells in the peripheral blood. GVHD was graded according to the standard criteria [32]. All patients engrafted at a median of 18 days (range, 12 to 46) and 12 of them (34%) developed ≥2 grade acute GVHD.

BKV Monitoring and Antiviral Therapy

BKV replication in both urine and plasma was determined by polymerase chain reaction.

BK viruria was tested for all patients before transplantation and then once each week until 100 days after HSCT. A positive result was considered significant for values > 9 × 10^6 copies/mL.

Antiviral therapy with i.v. cidofovir at a dose of 5 mg/kg associated with probenecid was given weekly over 21 days to the first 15 patients with BK-

Table 1
Clinical Characteristics of Patients Treated with Fibrin Glue

Characteristic	n (%)
Patients	35
Age, median (range), yr	35 (18-54)
Male	15 (43)
Malignant disease	
Lymphoid	20 (60)
Myeloid	15 (40)
Type of allogeneic HSCT	
HLA-identical sibling	6 (18)
Matched unrelated donor	8 (24)
Umbilical cord blood	4 (12)
Haploidentical donor	17 (46)
Conditioning regimen	
Myeloablative TBF	29 (83)
Reduced-intensity TBF	2 (6)
Including CTX	4 (11)
Engraftment, median (range), d	18 (12-46)
Acute GVHD ≥ II grade	12 (34)
Onset of grade ≥ 2 HC, median (range), d	34 (8-146)
BK-positive viruria	
At time of HSCT	15 (44)
At time of HC onset	35 (100)
BK-positive viremia	
At time of HSCT (evaluable, n = 13)	3 (23)
At time of HC onset (evaluable, n = 12)	7 (58)
HC grade	
Grade II	11 (31)
Grade III	21 (60)
Grade IV	3 (9)
Peripheral blood counts at time of HC onset, median (range)	
Hb, g/dL	8.8 (6.9-13)
Neutrophils, × 10^3/mL	4.5 (.1-23.6)
Platelets, × 10^3/mL	30 (4-170)

TBF indicates thiotepa, busulfan, and fludarabine; CTX, cyclophosphamide; Hb, hemoglobin.
Data presented are n (%) unless otherwise indicated.