Efficacy and safety of intravesical fibrin glue instillation for management of patients with refractory hemorrhagic cystitis: 12-months results. A promising therapy for hemorrhagic cystitis

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INTRODUCTION

Hemorrhagic cystitis (HC) is a condition defined as the presence of hematuria and lower urinary tract symptoms (LUTS), irritative voiding symptoms, such as urgency, frequency, nocturia and pain or burning with urination (1). Radiotherapy (RT) for pelvic malignancies, including prostate cancer (2, 3), could be associated with the development of HC in up to 6.5% of patients, as result of bladder wall modification and neovascularization (4). However, HC may be a complication of hematological cancer treatment, too. Medication toxicity and immune-mediated hypersensitivity may lead to LUTS and bladder mucosae bleeding in 7 to 68% of patients treated with cyclophosphamide (5). In literature there are many possible treatments for HC. First line treatments are the most conservative and include hyperhydration, blood transfusions, transurethral three-way catheterization with continuous bladder irrigation, hyaluronic acid instillation and reversal of anticoagulation. Second line treatments also include endo-vesical instillation of several compounds (e.g. aluminum compounds, silver or formalin) as well as transurethral surgery with laser or fulguration. In case of failure, third line options proposed include hyperbaric oxygen (HBO) or arterial embolization. In extreme cases a radical cystectomy with urinary derivation might be indicated (6-10). Despite the variety of treatments available there is not a consensus about the best treatment to use in these cases (11). More recently, FG endo-vesical application seems to be a promising therapy for HC (12, 13).

However, literature is limited to only two single center experiences (12, 13). Thus, we aim to report results about efficacy and safety of FG therapy in patients with HC.

MATERIALS AND METHODS

Patients and study population

We reviewed prospectively collected data from our insti-
Classification systems.

<table>
<thead>
<tr>
<th>Grade</th>
<th>RTDG/EORTC HC Grading</th>
<th>HC Grading</th>
<th>ICSI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Slight epithelial atrophy minor telangiectasia (microscopic hematuria)</td>
<td>Microscopic hematuria</td>
<td>Mild symptoms 0-6</td>
</tr>
<tr>
<td>Grade II</td>
<td>Moderate frequency generalized telangiectasia intermittent macroscopic hematuria</td>
<td>Macroscopic hematuria</td>
<td>Moderate symptoms 7-14</td>
</tr>
<tr>
<td>Grade III</td>
<td>Severe frequency and dysuria severe generalized telangiectasia (often with petechial), Frequent hematuria reduction in bladder capacity (&lt;150 cc)</td>
<td>Hematuria with clots requiring transfusion support</td>
<td>Severe symptoms 15-20</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Necrosis/contracted bladder (capacity &lt; 100 cc) Severe hemorrhagic cystitis</td>
<td>Macroscopic hematuria with clots and impaired renal function</td>
<td>–</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death for uncontrollable hematuria</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

HC: Hemorrhagic cystitis; EORTC: European organization for research and treatment of cancer/RTDG: Radiation therapy oncology Group grading of hematuria events due to radiotherapy; ICSI: Interstitial Cystitis Symptoms Index.
A total of 10 patients were treated. The 30% (n = 3) had HC secondary to bone marrow graft for hematological diseases after systemic chemotherapy treatment, the remaining 70% (n = 7) were diagnosed with actinic cystitis due to prostate cancer RT. The median age was 70 years (IQR 49.0-81.8). In the hematological patients median age was 45 years (IQR 36.0-45.5), while in the radio therapy patients group the median age was 75 years (IQR 70.0-84.5). The median onset time of hematuria was 4.8 (IQR 3.9-6.3) years after RT and 35 (IQR 27.5-62.5) days after hematological treatment. Main pre-operative and post-operative laboratory findings are reported in Table 2.

Of all, 5 patients (55%) had a complete response (no hematuria or other symptoms), 3 patients (33%) had only clinical response (improvement or absence of symptoms, grade < 2 hematuria) and one of them required catherization and bladder irrigation. Three patients required blood transfusions. One patient died immediately after the loco-regional anesthesia for complications not related to the procedure. Only one patient needed a second FG instillation eleven days after the first one, due to grade 3 hematuria and achieving a clinical response after the second instillation dose. Median hospital stay was 3 (IQR 1-6) days. No adverse events related to the procedure were recorded. Moreover, we recorded a reduction of the median ICSI after treatment. Indeed, the median ICSI was 13.0 (IQR 11.0-15.0) pre-operatively and 4.0 (IQR 2.0-5.0) postoperatively (p = 0.02). During the median follow up of 12 months, two patients died due to the progression of their hematological condition. None of the others required additional treatment for hematuria. Descriptive features and results of included patients are reported in Table 3.

### Table 2.
Pre-operative and post-operative (at discharge) patients’ blood count.

<table>
<thead>
<tr>
<th>Preoperatively</th>
<th>Postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells count (×10^6/mm³)</td>
<td>Hemoglobin (g/dl)</td>
</tr>
<tr>
<td>1</td>
<td>4.74</td>
</tr>
<tr>
<td>2</td>
<td>4.04</td>
</tr>
<tr>
<td>3</td>
<td>2.97</td>
</tr>
<tr>
<td>4</td>
<td>4.53</td>
</tr>
<tr>
<td>5</td>
<td>2.91</td>
</tr>
<tr>
<td>6</td>
<td>2.76</td>
</tr>
<tr>
<td>7</td>
<td>3.15</td>
</tr>
<tr>
<td>8</td>
<td>2.87</td>
</tr>
<tr>
<td>9</td>
<td>4.63</td>
</tr>
<tr>
<td>10</td>
<td>4.14</td>
</tr>
</tbody>
</table>

### Table 3.
Descriptive features of included patients treated with endovesical instillation of Vivostat®.

<table>
<thead>
<tr>
<th>Age</th>
<th>Grade of HC pre</th>
<th>RTDG/ EORTC pre</th>
<th>Primary</th>
<th>Cause of HC</th>
<th>Time from prior intravesical</th>
<th>Grade of hematuria (post-op)</th>
<th>RTDG/ EORTC post</th>
<th>Response</th>
<th>Hospital stay days</th>
<th>ICSI PRE</th>
<th>ICSI POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>2</td>
<td>3</td>
<td>PC</td>
<td>IMRT</td>
<td>Hyperhydration</td>
<td>0</td>
<td>Complete</td>
<td>2</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>4</td>
<td>4</td>
<td>PC</td>
<td>IMRT</td>
<td>Bladder irrigation, Catheterism, Blood transfusions</td>
<td>0</td>
<td>Complete</td>
<td>3</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>3</td>
<td>4</td>
<td>PC</td>
<td>IMRT</td>
<td>Bladder irrigation, Catheterism, Blood transfusions</td>
<td>3 1 after II treatment</td>
<td>Clinical 2 instillations</td>
<td>26</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>85</td>
<td>2</td>
<td>3</td>
<td>PC</td>
<td>IMRT</td>
<td>Catheterism</td>
<td>0</td>
<td>Complete</td>
<td>3</td>
<td>UC</td>
<td>UC</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>3</td>
<td>–</td>
<td>LLA</td>
<td>HSCT</td>
<td>35 days</td>
<td>Catheterism, Bladder irrigation</td>
<td>1</td>
<td>Clinical</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>2</td>
<td>–</td>
<td>LH</td>
<td>HSCT</td>
<td>3 months</td>
<td>Catheterism</td>
<td>0</td>
<td>Complete</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>84</td>
<td>3</td>
<td>4</td>
<td>PC</td>
<td>IMRT</td>
<td>5 years</td>
<td>Catheterism, Blood transfusions</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>3</td>
<td>–</td>
<td>UMA</td>
<td>HSCT</td>
<td>20 days</td>
<td>Bladder irrigation, Hyperhydration</td>
<td>0</td>
<td>–</td>
<td>Clinical</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>85</td>
<td>3</td>
<td>3</td>
<td>PC</td>
<td>IMRT</td>
<td>Catheterism, Bladder irrigation</td>
<td>0</td>
<td>Complete</td>
<td>4</td>
<td>UC</td>
<td>UC</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>3</td>
<td>3</td>
<td>PC</td>
<td>IMRT</td>
<td>Bladder irrigation, Catheterism</td>
<td>1</td>
<td>Clinical</td>
<td>4</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
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### Results
A total of 10 patients were treated. The 30% (n = 3) had HC secondary to bone marrow graft for hematological diseases after systemic chemotherapy treatment, the remaining 70% (n = 7) were diagnosed with actinic cystitis due to prostate cancer RT. The median age was 70 years (IQR 49.0-81.8). In the hematological patients median age was 45 years (IQR 36.0-45.5), while in the radio therapy patients group the median age was 75 years (IQR 70.0-84.5). The median onset time of hematuria was 4.8 (IQR 3.9-6.3) years after RT and 35 (IQR 27.5-62.5) days after hematological treatment. Main pre-operative and post-operative laboratory findings are reported in Table 2.

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### Discussion
Hemorrhagic cystitis is a urological condition that can meaningfully affect patients’ quality of life. Several ther-
apuetic options are available for HC treatment, however neither AUA nor EAU defined specific guidelines for the treatment of HC (11, 17). The treatment paradigm includes as first line treatment a noninvasive procedure attempting to reduce hematuria while supporting patients’ general condition, such as hyperhydration, blood transfusion, transurethral three-way catheterization, and continuous bladder irrigation (6).

In our study we investigated the results that could be obtained with the use of FG in HC patients’ treatment after that first line treatments have failed. Our results showed that a good bleeding control could be achieved with FG endo-vesical instillation with no adverse events, no major complication as ureteral orifice closure and hydrenephrosis were recorded in our experience. In case of injection near the ureteral orifice the use of a ureteral open-end catheter is recommended to reduce the risk of iatrogenic ureteral occlusion. Moreover, our results suggest that the use of FG endo-vesical instillation is related with a meaningful improvement in quality of life as proven by the improvement in ICSI score. Moreover, our study showed that the procedure is repeatable and that results are reliable over time as showed by our relative long follow-up of approximately 12 months.

The use of FG as a hemostatic agent have been previously studied in urological surgery and the use of the Vivostat® system have been proven to be effective and safety when applied to urological surgery, in particular to prevent bleeding in renal surgery and lymphatic leakage in lymphadenectomy (18-21). However, only few studies investigated its use for the treatment of HC. Specifically, Bove et al. have investigated the effectiveness of FG treatment in patients with actinic cystitis with hematuria refractory to standard treatment. Their experience was based on a series of 20 patients who developed HC following RT for different types of pelvic cancer: bladder cancer (30%), prostate cancer (35%) or gynecological cancer (35%) (13). They concluded that the endoscopic application of FG is a safe and effective therapeutic alternative for the treatment of HC refractory to conventional therapy because FG adheres tenaciously to the damaged mucosa, prevents the worsening of the inflammatory process from urine exposure and allows the tissue repair process. The endo-vesical application during cystoscopy allows a better view of the bleeding points and a better adhesion of the glue to the damaged mucosa due to the constant intravesical pressure (13).

Unfortunately, Bove and colleagues included only patients with actinic cystitis, conversely in the current report we also included patients with HC related to hematological conditions. This is of importance since the HC related to allogeneic hematopoietic cell transplantation negatively affects patient’s quality of life with an increased risk of death (22, 23). Currently its therapy was studied by Tirindelli et al. (12) on 35 patients who developed grade ≥ 2 HC not responsive to conventional therapy. Complete remission, defined as a regression of all symptoms and the absence of hematuria, was achieved in 100% of the cases at 7 days and 83 ± 7% at 50 days from the FG’s instillation. The 6-month survival rates of patients with HC was 49 ± 8% overall. Instead, if we consider only patients with complete clinical remission the 6-month survival rates were 59 ± 9%.

The results of this study suggest that the endoscopic application of FG should be considered a safe, non-invasive, easily repeatable, and inexpensive option for the management of HC in fragile and immunocompromised patients.

When considering other options, hyperbaric oxygen HBO is a widely used treatment. However, success rates are lower than ours (34-87.5% vs. 88% of our experience) with FG (6). Browne et al. in a literature review reported a successful rate without recurrences of 74% after HBO. They also reported that the main complication of this treatment was otalgia, occurred in 33% of patients (7). Intravesical instillation of various substances such as formalin, aluminum salts or hyaluronic acid is also reported. For instance, Pascoe et al. reported a success rate instillation therapy with formalin of 60-90% vs. 88% of our experience. However, authors reported serious side effects related to the use of formalin, including death in 2-4% of the cases. More specifically, Browne et al. also demonstrated the danger of formalin by recording adverse events, such as bilateral hydrenephrosis with anuria, vesico-vaginal fistula, and death in 30% of patients. The same study showed a success rate with hyaluronic acid instillation of 97% (7). Conversely, we reported no adverse events directly related to treatment. The only death reported was due to the general compromitted status of the patient and not to the FG application.

Aluminum salts were also used. However, its use is considered less effective than other endo-vesical treatment, but it is also affected by side effects: 38% of patients showed bladder spasms, transient delirium, urinary tract infections. The success rate was 60% (only 54% of responders had a durable response).

Imperatore et al. described the use of hyaluronic acid and chondroitin sulfate endo-vesical instillation treatment in 20 patients with refractory Bacillus Calmette-Guerin (BCG) induced chemical cystitis. The study showed an improvement in terms of bladder pain, urinary urgency, urinary volume per void and urinary frequency.

The clinical efficacy described in 19/20 patients had a statistically significative improvement durable in time with a permanence of benefit up to one year after therapy suspension (VAS score on bladder pain and urgency significantly decrease from the baseline; mean number of voids/24 hour and mean urinary volume per void significantly improved from the baseline $p < 0.05$ with respect to baseline in both cases) (24).

In a recent study Musieri et al. analyzed the use of platelet-rich plasma (PRP) in patients with HC after HSCT, they showed an alternative endo-vesical autologous instillation therapy to treat HC in hematological patients. They studied 10 patients with HC post HSTC related to BK virus infection, all patients underwent PRP instillation after electrocoagulation of the bleeding areas. No intraoperative complications were recorded, postoperative complications Clavien-Dindo Grade II occurred in 6 patients: 3 patients required additional blood transfusion, 3 patients required antibiotic therapy. One patient was readmitted for massive hematuria. 6 patients...
had complete response, 3 partial response and one no response. It seems to be a promising treatment option but related to a higher risk of complication compared to our technique with a similar success rate but in a highly selected group of patients (25).

In summary our study showed that the use of FG in HC patients is safe and effective with higher success rates and lower complications than other second line treatments. Despite the limited number of patients and the lack of a control group, in our study we point out that FG treatment is a promising treatment option also in the group of hematological patients with HC.

The main limitation of our study is the small number of patients included and the absence of a control group. In consequence, we are not able to infer if the use of FG treatment could lead to better result than any other conservative treatment and future prospective multicenter study are warrant. However, the same limitation applies also to other studies that included only few more patients. In addition, due to the small number of patients included we were not able to test the effect of FG treatment on HC in analyses adjusted for possible confounders, such as age or primary cause of HC. It might be possible that the effect of FG might differ based on the baseline characteristics of included patients as a consequence of the compound interaction with the host environment. It is also possible that the coagulation cascade promotion based on FG effect might differ in younger vs. older patients. Future studies should investigate also molecular aspects of FG instillation. Furthermore, we evaluated patients’ quality of life with ICSI score. However, other more specific scores about the quality of life in patients affected by malignancy (such as the EPIC score) would be more insightful (26). In future studies it should be included and evaluated to better clarify patients’ quality of life. Finally, we investigated only the clinical presentation of HC without any molecular or laboratory tests that could shed a light on the pharmacodynamic of FG application in HC cases. Indeed, literature is poor of evidence in this field and future studies should focus also on these aspects.

CONCLUSIONS

Autologous FG may be a safe and effective noninvasive and repeatable treatment modality in patients with refractory HC. Our report showed its efficacy also in patients treated after HC related to hematological conditions treatments and was no related to any adverse event.

AUTHORS’ CONTRIBUTION

We would like to thank all the Urologists M. Marchioni, F. Silletta, C. d’Orta, G. Primiceri, A. Rizzoli, F. Berardinelli, L. Schips that recruited the urological patients, performed the surgical procedures and followed them during the follow-up. They also helped with the drafting of this manuscript. Thanks to the hematologist S. Santarone and A. Natella that recruited and followed the hematological patients during the follow-up, also for the contribution with the processing of the manuscript regarding the hematological therapies and pathologies.

Thanks to the laboratory doctors P. Di Gregorio and S. Verna that helped us with the preparation of the FG solution from patients own plasma. All authors read and approved the final version of the manuscript.

REFERENCES


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