ABSTRACT

Introduction: Hemorrhagic cystitis is a potentially life-threatening complication in patients receiving cancer therapy. This urologic emergency is commonly associated with the chemotherapeutic use of oxazaphosphorine alkylating agents. This report describes a case of hemorrhagic cystitis associated with dacarbazine treatment.

Case summary: A 63-year-old man with asymptomatic metastatic malignant melanoma received 3 cycles of dacarbazine (600–850 mg/m²) monochemotherapy, each 3 weeks apart. Two weeks after the third cycle, he presented with gross hematuria and mild dysuria. Physical examination revealed no significant finding. Hematuria was confirmed by urinalysis, and urinary infection was excluded by repeated urine cultures. Ultrasonography revealed diffuse bladder wall thickening with no discrete mass or ulceration. Cystoscopy findings revealed generalized inflammation and edema of the mucosa of the bladder, confirming the diagnosis of hemorrhagic cystitis. The patient’s gross hematuria continued for 2 weeks and then completely resolved with supportive care. Two weeks after complete resolution, the patient experienced 2 transient episodes of gross hematuria that lasted a few hours and subsided spontaneously.

Discussion: Dacarbazine is currently considered the standard first-line treatment in patients with advanced malignant melanoma. At standard prescribed doses (a single dose of 850–1000 mg/m² or 250 mg/m² for 5 days per cycle), dacarbazine is a reasonably well tolerated chemotherapeutic drug; nausea, vomiting, and myelosuppression are the most common adverse effects. Association of dacarbazine with hemorrhagic cystitis has not been reported previously (in a PubMed literature search from 1950–2006), and only 1 case report associates temozolomide (an analog of dacarbazine) with hemorrhagic cystitis.

Based on the Naranjo adverse drug reactions probability scale, an objective assessment revealed dacarbazine to be a probable cause of hemorrhagic cystitis in this case.

Conclusions: This case report suggests that dacarbazine at conventional doses was a probable cause of hemorrhagic cystitis. Regular urinalysis and early intervention are recommended, as a means of detecting early hematuria and subsequently reducing or discontinuing dacarbazine treatment. Adequate hydration before, during, and after dacarbazine administration may be useful in preventing this complication. (Clin Ther. 2007;29:1161–1165) Copyright © 2007 Excerpta Medica, Inc.

Key words: dacarbazine-induced hemorrhagic cystitis, chemotherapy, malignant melanoma.

INTRODUCTION

Hemorrhagic cystitis is a diffuse inflammation of the mucosa of the bladder, which can be a life-threatening complication in cancer patients. In particular, chemotherapy and radiation therapy are the cancer treatment modalities that account for the majority of cases...
of this urologic emergency. With an incidence varying between 7% and 68%, hemorrhagic cystitis remains a common problem in patients undergoing bone marrow transplantation, causing considerable morbidity and occasionally contributing to mortality.1,2

Oxazaphosphorine alkylating agents, such as cyclophosphamide and ifosfamide, are the chemotherapeutic agents most frequently associated with hemorrhagic cystitis. The exact mechanisms by which these agents damage the bladder wall are unknown, although their toxic metabolite, acrolein, is considered responsible.1 Other alkylating agents, such as busulfan and thiotepa, are antineoplastic drugs that also potentially induce hemorrhagic cystitis, particularly in high-dose regimens.3 The imidazotetrazines, including dacarbazine and temozolomide, are another class of alkylating agents.4 An English-language search of PubMed, conducted for the years 1950 through 2006 using the search terms dacarbazine and hemorrhagic cystitis, yielded no previous reports of an association between dacarbazine and hemorrhagic cystitis, and only a single case report associating temozolomide (an analog of dacarbazine) with hemorrhagic cystitis.5 In the present report, we describe a case of hemorrhagic cystitis in a patient receiving conventional dosing regimens of dacarbazine.

CASE SUMMARY
A 63-year-old man with metastatic malignant melanoma of the foot was referred to our institution for systemic treatment. At the time of referral, the patient had multiple asymptomatic pulmonary metastases that were identified by chest radiograph and computed tomography scan. The patient’s performance status was not impaired, and he had normal activity. On physical examination, he was fully conscious and had no difficulty with speech, vision, or respiration. His vital signs were as follows: respiratory rate, 14 breaths per minute; heart rate, 65 beats per minute; blood pressure, 125/85 mm Hg; and body temperature, 37.2°C. Body weight was 64 kg. Cardiopulmonary examination was unremarkable and there was no evidence of lymphadenopathy or organomegaly. His family and medical histories were unremarkable, and the patient was not receiving any medication. Abdominal and pelvic ultrasonography and computed tomography had shown no evidence of visceral metastasis. Admission biochemical examinations including complete blood count, liver function tests, blood urea nitrogen, serum creatinine, potassium, sodium, calcium, urinalysis, and coagulation tests (prothrombin and partial thromboplastin times) were within normal limits.

Single-agent chemotherapy with dacarbazine was considered as systemic treatment, and the patient received 3 cycles of dacarbazine monotherapy, each 3 weeks apart. The doses of dacarbazine in the first, second, and third cycles of chemotherapy were 600, 700, and 850 mg/m², respectively. During the course of chemotherapy, the patient had no significant complaints, and regular physical and biochemical examination revealed no abnormal findings. Within this period, he did not receive any other medication or treatment.

Two weeks after the third course of chemotherapy, the patient developed gross hematuria, confirmed with urinalysis. At that time, his vital signs were normal, and mild irritative voiding symptoms were his only complaint. Urine cultures excluded urinary infection. Abdominal and pelvic ultrasonography revealed diffuse bladder wall thickening with no discrete mass or ulceration. Cystoscopic examination revealed generalized inflammation and edema of the mucosa of the bladder, confirming the diagnosis of hemorrhagic cystitis. The patient’s laboratory findings are summarized in the table. Other common causes of hemorrhagic cystitis were excluded, and the patient received a diagnosis of chemotherapy-induced hemorrhagic cystitis. A 16-French Foley urinary catheter was inserted into the bladder, and saline lavage was initiated. He then underwent oral and intravenous hydration. The gross hematuria continued for 2 weeks without hemoglobin drop or the need for blood transfusions, and then stopped completely. During the first month of follow-up and 2 weeks after complete resolution of the gross hematuria, the patient experienced 2 transient episodes of gross hematuria, each lasting a few hours and subsiding spontaneously. Three months later, he developed brain metastases, refused palliative cranial radiation therapy, and died from these metastases.

DISCUSSION
Cancer therapy may cause life-threatening complications and sequelae requiring preventive care, prompt evaluation and diagnosis, and urgent institution of treatment.5–10 Urologic emergencies, in particular hemorrhagic cystitis, are relatively common problems in cancer patients receiving cancer therapy; the incidence
is particularly high after allogeneic bone marrow transplantation and may reach up to 70% without preventive measures. In immunocompromised patients, hemorrhagic cystitis commonly results from toxic metabolites of chemotherapeutic agents, radiation therapy, and viral infection, which account for >90% of cases. This urologic emergency can cause considerable morbidity, lead to renal toxicities, prolong hospitalization, increase health care costs, and occasionally contribute to death.

Hemorrhagic cystitis is a well-described complication of cancer treatment for patients undergoing hematopoietic stem cell or bone marrow transplantation (occurring in 7%–52% of recipients), and is generally attributed to high-dose cyclophosphamide or busulfan in the conditioning regimen. Urothelial toxicity from oxazaphosphorines is cumulative and generally dose related. Although it is a common problem in cancer patients receiving high-dose regimens of oxazaphosphorine alkylating agents, urothelial toxicity may occur with conventional dosing as well. The incidence of hemorrhagic cystitis has been reported to be 7% to 12% in patients receiving conventional doses of oxazaphosphorine alkylating agents, and 7% to as much as 68% in patients undergoing bone marrow transplantation.

There is only a single case report describing temozolomide-related hemorrhagic cystitis in a patient in whom this agent was successfully used to treat radiation refractory metastatic brain tumors arising from primary breast cancer. Hemorrhagic cystitis in this case developed after the second cycle of temozolomide treatment. A promising new imidazotetrazine derivative, temozolomide is used for the treatment of malignant melanoma, particularly with brain metastases and primary gliomas of the central nervous system.

A single dose of 850 to 1000 mg/m² of dacarbazine (also known as DTIC, dimethyl triazeno imidazole carboxamide), or a multiple-dose regimen of 250 mg/m² IV for 5 days per cycle, is considered the first-line treatment for patients with metastatic melanoma. Because the single dose of dacarbazine appears to be well tolerated and to deliver clinical improvements comparable to multiple-dose regimens providing the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, %</td>
<td>44.2</td>
<td>42–52</td>
</tr>
<tr>
<td>White blood cell, 10⁹/L</td>
<td>6.6</td>
<td>4.0–10.5</td>
</tr>
<tr>
<td>Platelet, 10⁹/L</td>
<td>263</td>
<td>150–450</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>14</td>
<td>8–23</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.8</td>
<td>0.8–1.2</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>137</td>
<td>136–142</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>3.9</td>
<td>3.9–5.3</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>8.8</td>
<td>8.9–10.7</td>
</tr>
<tr>
<td>Phosphate, mg/dL</td>
<td>2.7</td>
<td>2.8–4.6</td>
</tr>
<tr>
<td>Blood sugar, mg/dL</td>
<td>105</td>
<td>60–105</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.6</td>
<td>3.7–5.6</td>
</tr>
<tr>
<td>Bilirubin, total, mg/dL</td>
<td>0.4</td>
<td>0.1–1.2</td>
</tr>
<tr>
<td>Bilirubin, conjugated, mg/dL</td>
<td>0.2</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Alkaline phosphates, U/L</td>
<td>227</td>
<td>65–260</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>12</td>
<td>15–45</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>3</td>
<td>10–40</td>
</tr>
<tr>
<td>Prothrombin time, min</td>
<td>13</td>
<td>±2 sec*</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1</td>
<td>0.8–1.2</td>
</tr>
<tr>
<td>Partial thromboplastin time, min</td>
<td>31</td>
<td>25–38</td>
</tr>
<tr>
<td>Urine culture</td>
<td>No growth</td>
<td>No growth</td>
</tr>
</tbody>
</table>

*Control should be 11–18 sec.
same dose per cycle, the single dose is recommended for the treatment of patients with metastatic malignant melanoma without brain metastases. At standard prescribed doses, severe adverse effects such as aplastic anemia and fulminant hepatitis are rare and occur in <1% of patients receiving dacarbazine chemotherapy. Constitutional symptoms such as nausea and vomiting are the most frequent complaints, occurring in 90% of patients. A moderate myelosuppression is usually observed after dacarbazine administration in 25% to 50% of patients.

This is the first reported case of hemorrhagic cystitis related to dacarbazine chemotherapy in a patient with metastatic malignant melanoma. An objective causality assessment using the Naranjo adverse drug reactions probability scale revealed a probable relationship between hemorrhagic cystitis and dacarbazine in this case.

Hemorrhagic cystitis has a heterogeneous clinical course that ranges from asymptomatic microscopic hematuria to massive bleeding necessitating blood transfusions, with or without obstructive renal failure. Gross hematuria and irritative voiding symptoms, such as dysuria with frequency and urgency, are the most common clinical presentations. Biochemical values of the coagulation profiles and platelet count are generally normal, and urine culture is negative. Cystoscopic findings reveal acutely diffuse inflammation as increased vascularity with fragile “corkscrew” vessels.

No clinical predictors have identified which patients will experience this complication. Prevention of hemorrhagic cystitis, based on general and specific measures, should be considered; however, it is not always effective.

Chemotherapy-induced hemorrhagic cystitis usually occurs during or immediately after cancer chemotherapy, but it may develop any time after chemotherapy administration. In most instances, the hematuria resolves within several days after cessation of the chemotherapy agents, but it may persist for months.

The current optimal treatment of chemotherapy-induced hemorrhagic cystitis in cancer patients involves a combined approach that includes preventive measures and early intervention with aggressive supportive care. Management of hemorrhagic cystitis is usually initiated by discontinuing or reducing the responsible drug. Intensive intravenous hydration and forced diuresis are routinely used to dilute urinary toxic metabolites and minimize their toxicity. Urothelial toxicity also can be minimized by administering a uroprotective agent such as sodium 2-mercaptopropanesulfonate (mesna), which reduces the incidence of hematuria and hemorrhagic cystitis in cancer patients receiving oxazaphosphorine-based chemotherapy. Intravesical instillation of formalin, alum, and prostaglandin E_1 and F_2 has been used to treat chemotherapy-induced hemorrhagic cystitis. Systemic administration of conjugated estrogen, hyperbaric oxygen treatment, and the use of local yttrium aluminum garnet laser therapy have been reported to be effective. Cystoscopic evacuation may be required for major clots that cannot be removed by irrigation. In cases of massive and life-threatening bleeding, surgical intervention such as cystectomy may be indicated.

CONCLUSION

We report a case of probable association of hemorrhagic cystitis with dacarbazine at conventional doses.

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REFERENCES


Address correspondence to: Mohammad Mohammadianpanah, MD, Department of Radiation Oncology, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, 71936, Iran. E-mail: mohpanah@sums.ac.ir