Review Article

Severe Hemorrhagic Cystitis

M. Comito and M. E. Trigg
Pediatric Bone Marrow Transplantation Program, Department of Pediatrics, University of Iowa College of Medicine, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

Abstract: Hemorrhagic cystitis is bleeding which originates from the bladder. Chemotherapy and radiation account for the majority of cases, but it can also result from a variety of drugs, infections, or a primary cancer. It is a significant problem after allogeneic bone marrow transplantation, and is associated with a high mortality rate. Bladder manipulations with instillations of alum, formalin, phenol, and silver nitrate have had limited success for cystitis after bone marrow transplantation. Prostaglandin bladder instillation is a simple bedside procedure that appears promising for this group of patients. While it is not a guaranteed treatment for all patients, it offers clear advantages over the previous treatments that were available. When prostaglandin bladder instillations fail, then surgical intervention with urinary diversion is justified.

Keywords: Bone marrow transplantation; Cyclophosphamide; Hemorrhagic cystitis; Prostaglandins

Introduction

Hemorrhagic cystitis is bleeding which originates from the bladder, and can be either acute or chronic. It is most commonly secondary to chemotherapy or radiation, but can also result from a variety of drugs, infections, or a primary cancer (Table 1). It is a frustrating problem for both oncologists and urologists, and produces diagnostic and therapeutic problems. Although it is uncommon, hemorrhagic cystitis can be a source of life-threatening hemorrhage. It is also a source of further iatrogenic complications with increased infectious risks secondary to bladder catheterization and multiple transfusions.

Chemotherapy and radiation account for the majority of cases of hemorrhagic cystitis. Patients who undergo bone marrow transplantation have a conditioning regimen that includes both of these agents, so this is a special group of patients who are at increased risk. Without appropriate prophylaxis, acute hemorrhagic cystitis occurs in 30% of bone marrow transplant recipients [1]. That which is induced by high-dose cyclophosphamide usually occurs within 48 hours and may persist for 2 months. Much of this can be prevented...
by the simultaneous administration of mesna and the use of hydration and diuresis. Nevertheless, hemorrhagic cystitis remains a serious problem in bone marrow transplantation, with an incidence of 20%–21% [2,3]. These patients have extended, difficult hospitalizations and an overall mortality rate of 30%–40% [4]. The incidence of severe hemorrhagic cystitis with clots is estimated to be 2%–5% [4], with a mortality of up to 75% [5].

A significant number of cases of hemorrhagic cystitis after bone marrow transplantation are late-onset in nature and may be due to reactivation of a viral infection during the immunosuppressed phase. These are often difficult to treat despite numerous bladder manipulations. Previous bladder manipulations, which include instillations of alum, formalin, phenol and silver nitrate, have had some success with cystitis secondary to cyclophosphamide or radiation, but only limited success post bone marrow transplantation [6]. Recognition of a viral etiology is important because it may explain the apparent failure of interventions designed to eliminate cyclophosphamide-associated hemorrhagic cystitis.

The use of prostaglandins is a more recent method that shows some promise. Although the mechanism is largely unknown, it is postulated that prostaglandins may be cytoprotective to the urothelium and provide hemostasis by natural physiological mechanisms rather than fixation.

Severe hemorrhagic cystitis is a challenging problem, especially for those patients who have undergone an allogeneic bone marrow transplant in which it is associated with a high mortality rate. In this paper we will review the etiology and treatment options, and then discuss a general treatment plan for acute hemorrhagic cystitis after bone marrow transplantation.

**Oxazaphosphorines**

Oxazaphosphorines are alkylating agents that were developed in an attempt to produce agents with a greater cytotoxic specificity and larger therapeutic indices than nitrogen mustard. Oxazaphosphorines are inactive prodrugs that need to be activated by the liver microsomes to become effective therapeutic agents. Cyclophosphamide in an oxazaphosphorine that is one of the most widely used anticancer drugs, because it has a broad range of clinical activity. It is also used in bone marrow transplant preparative regimens and as an immunosuppressant in non-neoplastic disorders. After its introduction in 1958, there soon were numerous reports concerning cystitis, a side effect not previously observed with other alkylating agents [7]. This cystitis consisted of frequency, urgency, dysuria, and microscopic and macroscopic hematuria. Sometimes this progressed to fulminating mucosal necrosis and hemorrhage [8]. The mortality rate secondary to massive uncontrolled bladder hemorrhage has been reported at 4% [9]. Subsequently other oxazaphosphorine agents were reported to have similar effects [10].

Because the bladder toxicity was identified as the major dose-limiting side effect of the oxazaphosphorine compounds, considerable effort was directed towards defining the causative agents. Early studies implicated the alkylating agents themselves, but Philips and associates demonstrated in a classic experiment that it was the intermediate agents of cyclophosphamide that were responsible for the cystitis [1]. They instilled cyclophosphamide directly into the bladder of a dog and no damage was done. When urine collected from dogs that had recently received cyclophosphamide was introduced by a catheter into a normal dog bladder, it induced the typical changes seen after intravenous administration. The bladder changes occurred rapidly within 24–48 hours, and consisted of ulceration of the mucosal epithelium, hemorrhage, and edema in all bladder tissues, as well as necrosis in the smooth muscles and small arteries. Thus, a direct toxic effect on the bladder mucosa by metabolites of cyclophosphamide was postulated. Subsequent work by Cox showed acrolein to be the causative agent [7]. By studying carefully chosen metabolites and analogues of cyclophosphamide, all the compounds that release acrolein were shown to be toxic to the bladder.

There have also been cytological studies of the urinary bladder in man, looking at the effect of cyclophosphamide [12]. The serial cytologic examination of the urinary sediment showed a degenerative process similar to that seen in radiation damage. The cytologic atypia did not necessarily correlate with the dose and may have been related more to the hydration status of the patient. The cytologic findings are also not specific, in that similar changes can also be seen after catheterization and viral infection. In those patients who underwent cystoscopy for cyclophosphamide-induced cystitis, a majority had abnormal findings of mucosal erythema, ulceration, small-vessel hemorrhage and reduced bladder capacity. When these patients were recystoscoped after resolution of their cystitis, the bladder mucosal abnormalities persisted [8].

Early studies looking at ways to prevent cyclophosphamide-induced cystitis focused on hydration with forced diuresis. Philips showed that most bladder damage occurred early and could be prevented by promoting a brisk diuresis during the first few hours after administration, presumably by diluting the toxic components [11]. Further studies looking at forced diuresis and frequent voiding, as well as continuous catheter drainage, showed that there was no decrease in therapeutic effect of cyclophosphamide with the forced diuresis, or an increase in infection with catheter use [5]. The use of continuous catheter drainage for 48 hours post-cyclophosphamide may only be useful in preventing acute cystitis, but may not decrease episodes of late-onset cystitis.

Because of the unpredictable response to hydration and diuresis, other methods of uroprotection were sought. Various thiols have been tested for their chemical protective properties against alkylating agents [13]. N-acetylcysteine was one of the first agents tested for