Risk Factors and Predictors of Severity Score and Complications of Pediatric Hemorrhagic Cystitis

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Abbreviations and Acronyms

BMT = bone marrow transplantation

CBI = continuous bladder irrigation

HC = hemorrhagic cystitis

PBSCT = peripheral blood stem cell transplantation

PRT = pelvic radiotherapy

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Purpose: We retrospectively analyzed our institutional incidence of hemorrhagic cystitis, identified risk factors, and examined associations of risk factors with disease severity and genitourinary complication rates.

Materials and Methods: We reviewed charts of all consecutive pediatric patients treated from 1986 to 2010. We analyzed demographics, underlying diagnosis and treatment data to assess risk factors for hemorrhagic cystitis. We also correlated disease severity scores with clinical predisposing factors, and performed univariate and multivariate analyses to examine associations between risk factors and outcomes.

Results: Hemorrhagic cystitis was observed in 97 of 6,119 children (1.6%), most of whom (75%) had severity scores of II or III. Mean ± SD age was 12.2 ± 6.3 years for patients with hemorrhagic cystitis and 10.5 ± 7 years for patients without hemorrhagic cystitis ($p = 0.017$). On univariate analysis increased risk of hemorrhagic cystitis was significantly associated with age greater than 5 years, male gender, cyclophosphamide or busulfan chemotherapy, bone marrow or peripheral blood stem cell transplantation, pelvic radiotherapy and underlying diagnoses of rhabdomyosarcoma, acute leukemia and aplastic anemia. On multivariate analysis age greater than 5 years, allogeneic bone marrow or peripheral blood stem cell transplantation and pelvic radiotherapy were significantly associated with increased risk of hemorrhagic cystitis. Older age, late onset hemorrhagic cystitis, positive urine culture for BK virus and bone marrow or peripheral blood stem cell transplantation were associated with greater disease severity. Patients with higher severity scores more frequently experienced bladder perforation, hydronephrosis, overall hemorrhagic cystitis complications, and increased creatinine and blood urea nitrogen levels during followup.

Conclusions: Older age, previous bone marrow or peripheral blood stem cell transplantation and BK virus in the urine are risk factors for hemorrhagic cystitis and are associated with a higher severity score. Higher severity scores are associated with increased rates of genitourinary complications and renal impairment.

Key Words: cystitis, hematuria, pediatrics, risk factors, urologic surgical procedures

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HEMORRHAGIC cystitis is a diffuse inflammatory condition of the bladder that is characterized by sustained hematuria and lower urinary tract symptoms secondary to diffuse vesical bleeding.[1,2] Its severity, which is commonly graded according to criteria proposed by Droller et al,[3] can range from mild hematuria that may resolve spontaneously to a potentially life-threatening presentation with significant morbidity requiring numerous interventions. Hemorrhagic cystitis can occur after bone marrow or peripheral blood stem cell transplantation, pelvic radiotherapy and administration of certain alkylating chemotherapeutics, and after infection with polyomavirus, adenovirus or cytomegalovirus.[2] However, it remains unclear how potential risk factors affect disease severity. In this retrospective study we assessed predisposing factors for hemorrhagic cystitis, elucidated their influence on symptom severity, and examined associations between disease severity and patient outcomes.

METHODS

After obtaining institutional review board waiver of patient informed consent requirements, we searched our database for all pediatric (0 to 21 years) oncologic cases managed from January 1986 through July 2010. The charts of patients with hemorrhagic cystitis were reviewed for demographics, underlying diagnoses, chemotherapeutic regimens, PRT or total body irradiation, BMT/PBSCT, urine bacterial and viral cultures, complete blood count, hemorrhagic cystitis severity score, response to hemorrhagic cystitis treatment, complications and renal function throughout followup. HC was defined as presence of sustained macroscopic or microscopic hematuria and symptoms of bladder irritability such as dysuria, frequency and urgency in the absence of a urinary tract infection. Severity scores were based on previously published criteria (supplementary Appendix, http://jurology.com/).[3] At our institution urine assays for patients with HC include bacterial and viral culture, and electron microscopy for polyomavirus. Patients with radiological evidence of renal or bladder calculi or tumors invading the bladder wall were excluded from the study.

In all patients HC prevention during conditioning regimens consisted of hyperhydration administered as a continuous infusion of at least 3,000 ml/m^2 fluids daily. Sodium-2-mercaptoethanesulphonate (mesna) was often coadministered with chemotherapy regimens containing cyclophosphamide or ifosfamide.

Our treatment algorithm for pediatric HC is presented in the figure. Initially, supportive therapies were performed to increase urine output for prevention of clot formation and any consequent urinary obstruction. These measures included hyperhydration, forced diuresis, and blood and platelet transfusions, as needed, to maintain a platelet count greater than 50,000. If necessary, coagulopathy correction was also performed. Urinary symptoms were managed by administration of phenazopyridine and oxybutynin. Continuous bladder irrigation was started for 3 to 7 days for grade III HC that was unresponsive to initial supportive therapy. If CBI was ineffective, large clots were identified on ultrasound or obstructive uropathy was evident, the patient underwent cystoscopy, blood clot removal and cauterization of any identifiable focal bleeding areas. In cases of diffuse bleeding on cystoscopy, and after clot removal with saline irrigations, the bladder was instilled with a 2% solution of formalin after verifying the absence of vesicoureteral reflux or bladder perforation via cystography. This measure was commonly followed by placement of a three-way Foley catheter for CBI. If small urethra size precluded Foley catheterization, suprapubic catheter insertion was performed.

All statistical analyses were performed using SPSS® PASW Statistics GradPack software. Univariate analysis was conducted using the chi-square method or Fisher exact test for qualitative variables and ANOVA for comparison of means, while multivariate analyses used logistic regression, with statistical significance defined as $p < 0.05$.

RESULTS

Clinical Features

A total of 6,119 pediatric patients underwent chemotherapy, BMT/PBSCT or PRT for various malignant and nonmalignant diseases. HC developed in 97 patients (1.6%), manifesting at a mean ± SD interval of 2.7 ± 4.9 months (range 1 day to 23 months) following induction of BMT/PBSCT and 12.4 ± 18.9 months (8 days to 6 years) following latest PRT. Demographics, underlying diagnoses and administered treatments are summarized in the supplementary table (http://jurology.com/). BK virus assays were frequently performed on suspicion of HC but were not systematically performed across the entire population.

Nine patients had grade I HC (9.3%) with an average duration of 3 days (range 1 to 8). All patients responded to hyperhydration and none experienced further complications.

A total of 42 patients (43.3%) had grade II HC. Average symptom duration was 12 days (range 1 to 90) and initial treatment was hyperhydration. A total of 13 patients required placement of a Foley catheter for CBI, of whom 7 (53.8%) did not respond and required formalin instillation as definitive therapy. The only grade II HC complication was severe anemia (3 patients).

A total of 31 patients (32%) with grade III HC recovered within an average of 33 days (range 8 to 116). Associated complications included hydronephrosis (3 patients) and anemia (3). Of the patients 19 (61.3%) were unresponsive to hydration and CBI, and subsequently underwent cystoscopy, cauterization and 2% formalin instillation. Four patients required suprapubic catheterization to help maintain clear urine.