Risk Factors Associated with Severity and Outcomes in Pediatric Patients with Hemorrhagic Cystitis

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Abbreviations and Acronyms

BKaHC = BK virus associated HC

BMT = bone marrow transplantation

CBI = continuous bladder irrigation

GVHD = graft vs host disease

HC = hemorrhagic cystitis

PCN = percutaneous nephrostomy tube

XRT = external beam radiation therapy

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Purpose: Hemorrhagic cystitis is a complication of treatment of pediatric cancer with considerable variation in severity and morbidity. This study presents an analysis of hemorrhagic cystitis severity and treatment outcomes in a large pediatric population.

Materials and Methods: Patients with hemorrhagic cystitis treated at St. Jude Children's Research Hospital® were identified from 1990 to 2010. Demographic data were gathered along with information pertaining to initial primary diagnosis, hemorrhagic cystitis diagnosis and treatment, and mortality. Statistical analyses were performed to evaluate associations between risk factors and severity of hemorrhagic cystitis as well as treatment outcomes.

Results: Of the 285 patients who met inclusion criteria 54% were male. Mean age was 11.41 years. Mean time from initial primary diagnosis to hemorrhagic cystitis onset was 29 months. Noninvasive treatment was performed in 246 patients (86%) and operative intervention was required in 14 (4.9%). Bivariate analysis demonstrated that pelvic radiation therapy ($p = 0.0002$), any radiation therapy ($p = 0.005$), acute lymphocytic leukemia ($p = 0.01$), bone marrow transplantation ($p = 0.0225$), cyclophosphamide exposure ($p = 0.0419$) and BK virus positivity ($p = 0.0472$) were predictors of higher grade hemorrhagic cystitis. Factors correlating with the need for invasive management on bivariate analysis included pelvic radiation therapy ($p = 0.0266$), bone marrow transplantation ($p = 0.0007$), hematological malignancy ($p = 0.0066$), ifosfamide exposure ($p = 0.0441$) and male gender ($p = 0.0383$). Multivariate analysis showed independent effects of pelvic radiation therapy ($p = 0.001$) and delayed onset of hemorrhagic cystitis ($p = 0.0444$).

Conclusions: Severity of hemorrhagic cystitis and failure of noninvasive management correlate with several identifiable risk factors. Prospective identification of patients with these risk factors may allow for targeted early intervention in those at highest risk.

Key Word: urinary bladder, hemorrhage, cystitis, risk factors, treatment failure

HEMORRHAGIC cystitis is characterized by diffuse mucosal bleeding that develops secondary to chemotherapy, XRT, BMT and/or opportunistic infections.[1] There is considerable variability in the presentation, severity and treatment outcomes of patients with HC. Some patients experience

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only mild irritative symptoms with microscopic hematuria while others endure severe lower urinary tract symptoms, obstruction, urinary retention and/or life threatening hemorrhage. Conservative measures, including medications, intravenous fluids, diuresis and antiviral treatment, may be effective for many cases of HC.[2] Patients with more severe HC may require CBI and/or operative intervention such as endoscopic or open clot evacuation, intravesical coagulant instillation, hypogastric artery embolization or urinary diversion with percutaneous nephrostomy. The consequences of these interventions may cause considerable morbidity and mortality, and may necessitate subsequent complex reconstruction, including cystectomy in rare cases.[3] Because the clinical course of HC is highly variable, it can be difficult to determine the optimal approach for each patient.

Published series have documented the variation that exists among patients with HC.[1,4] Due to the rarity of HC these series are relatively small and focused on specific groups at risk, such as patients with BMT. We report an analysis of HC severity and treatment outcomes in the pediatric population at St. Jude Children's Research Hospital. We hypothesized that there are characteristics of patients with HC that may predict the outcome of the disease and identifying these predictors may guide management.

METHODS

After receiving institutional review board approval we reviewed the charts of patients at St. Jude Children's Research Hospital in whom HC developed from 1990 to 2010. Patients were identified using ICD-9 codes for cystitis and hematuria (595, 599.7, 599.71 and 599.72). Study exclusion criteria included multiple malignancies, nonmalignant primary disease without XRT or BMT and age 18 years or greater at initial diagnosis of primary disease. HC grade was scored using the scale proposed by Droller et al (see Appendix).[5] Demographics recorded included race, gender, age at primary diagnosis and age at HC onset. Data on primary diagnosis, HC diagnosis and treatment, BMT, XRT, chemotherapy regimen, BK virus status, transfusion and death were collected. Bivariate analyses were performed using simple logistic regression models in addition to generalized and cumulative logit models. A stepwise model selection procedure was used to produce models for multivariate analyses. Some categorical variables were combined when sample size precluded individual assessment. ROC curves were developed in an attempt to define relevant cutoff points for continuous variables. SAS® 9.3 was used for all analyses.

RESULTS

At St. Jude Children's Research Hospital 4,071 pediatric patients with primary cancer diagnoses were seen from 1990 to 2010. A total of 285 patients were identified with HC. Of the patients 247 had a primary cancer diagnosis, representing 6% of all patients with cancer. HC developed in 38 patients following BMT for noncancer primary diagnoses. Supplementary table 1 (http://jurology.com/) shows patient demographics, initial diagnoses and age at onset of HC. BMT was done in 212 patients (74%). Cyclophosphamide or ifosfamide exposure occurred in 236 patients (83%) and 157 (55%) received XRT. HC was grade I, II, III and IV in 114 (40%), 99 (35%), 58 (20%) and 14 patients (5%), respectively. HC onset occurred a median of 10.8 months after initial primary diagnosis with a right skewed distribution (see figure). Supplementary tables 2 and 3 (http://jurology.com/) show HC grade and treatment outcome distributions.

Several factors were significant predictors of HC severity. On bivariate analysis pelvic XRT showed the greatest association with a OR of 20.615 for higher grade HC compared to nonirradiated patients. Any XRT (including whole body and targeted XRT) was associated with a OR of 1.866. Acute lymphocytic leukemia conferred a OR of 4.128 for higher grade HC compared to other leukemias. Treatment with BMT conferred a OR of 2.536. Cyclophosphamide exposure (OR 1.73) and BK virus positivity (OR 1.835) also showed effects (table 1).

A trend was noted of an association of age at HC onset with higher HC grade, although it was not statistically significant ($p = 0.0721$). Platelet count, hemoglobin, gender and race had no significant effect on HC grade. To assess for possible confounders or overlapping variables multivariate analysis was performed, which required grouping categories due to small sample size. The odds of high grade (III and IV) and low grade (I and II) HC were compared and demonstrated a persistent independent effect from pelvic XRT (OR 15.784, $p = 0.0011$). Other factors did not retain significance in the multivariate model (table 1).

A total of 246 patients (86%) were treated conservatively with observation or medical management (hyperhydration, anticholinergics and antivirals as indicated), 25 (9%) required CBI, 14 (5%) required operative intervention consisting of cystoscopy with clot evacuation with or without fulguration and 6 (2%) required additional anticoagulant instillation with silver nitrate, alum or formalin. One patient received PCNs to enable autotamponade of the bladder.

The need for invasive management for HC was statistically associated with several factors. Operative intervention was associated with pelvic XRT (OR 15.99) and male gender (OR 4.107) on bivariate analysis. CBI was associated with BMT (OR 10.753), ifosfamide exposure (OR 3.601) and hematological