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Clostridium Difficile Infection after Allogeneic Hematopoietic Stem Cell Transplant: Strain Diversity and Outcomes Associated with NAP1/027

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) recipients are at high risk for developing *Clostridium difficile* infection (CDI). We studied the incidence, risk factors, NAP1/027 prevalence, and clinical outcomes, including acute lower gastrointestinal graft-versus-host disease (GI GVHD), associated with early CDI in this population. A retrospective review was conducted of patients who underwent allogeneic HSCT at Memorial Sloan Kettering Cancer Center from January 1, 2005 to September 30, 2010. Early CDI was defined as infection occurring from day −10 to day +40 from stem cell infusion. Among 793 patients who received allogeneic HSCTs, early CDI occurred in 11.9%; 56% cases were between day −5 and day +5. Overall incidence was 25.2 cases/10,000 at-risk days. There was a high prevalence of NAP1/027 strains during peak incidence (61% in 2008). NAP1/027 was the most common strain in both adult and pediatric cases (24% and 23%, respectively). CDI was clinically mild, including those due to NAP1/027. Metronidazole was the primary treatment for 91 of 94 patients, 7 of 8 cases refractory to metronidazole had no response to vancomycin, and none was due to NAP1/027. Relapse of CDI was common (31%). The cumulative incidence of GI GVHD in patients with and without early CDI was 6.8% and 8%, respectively ($P = .5$). Most cases of CDI occurred during conditioning or immediately after transplant. Despite high prevalence of NAP1/027, we found only mild disease. Most patients were treated successfully with metronidazole, irrespective of NAP1/027 status. There was no significant association between early CDI and subsequent development of GI GVHD. This study demonstrates the high incidence of CDI early after allogeneic HSCT with wide diversity among infecting strains. Despite the high prevalence of NAP1/027, the disease is mild but relapses are common. No association was found between CDI and subsequent development of GI GVHD.

INTRODUCTION

Patients undergoing hematopoietic stem cell transplantation (HSCT) are particularly at risk for *Clostridium difficile* infection (CDI) because of the extended length of stay for transplant, frequent antibiotic use, and an immunocompromised state. *C. difficile* rates as high as 12.5% to 27% have been described in allogeneic HSCT recipients, a risk 15 to 20 times greater than other hospitalized patients [1-6], including solid organ transplant recipients.

Despite the rising incidence of CDI since the emergence of the NAP1/027 strain, the prevalence and impact of infection with this particular strain among allogeneic HSCT recipients has never been examined [7,8]. Although the frequency of CDI is much higher among allogeneic HSCT recipients when compared with autologous stem cell and solid organ transplantation recipients, the disease is reported to be mild in allogeneic HSCT recipients [2,9-12]. Despite this, immunocompromising conditions have been associated with severe CDI. As a consequence, some experts recommend vancomycin as first-line therapy for CDI because of the inability to accurately apply clinical scoring systems that measure severity of CDI in this population [13,14]. CDI has also been implicated in the development of acute gastrointestinal graft-versus-host disease (GI GVHD), postulated to be

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triggered by disruption of mucosal barriers and release of proinflammatory cytokines. However, no conclusive evidence has supported this hypothesis [1,12,15].

We examined the incidence, molecular epidemiology, and clinical characteristics of early CDI, especially in relation to occurrence of the NAP1/027 strain. We also explored the potential relationship between early CDI and subsequent development of GVHD, with a focus on grade II or higher acute lower GI GVHD, in a large cohort of allogeneic HSCT recipients. The study population included patients that had received conventional T cell–depleted and cord blood allografts.

METHODS

Study Design and Patient Population

This is a retrospective review of 793 adult and pediatric patients who underwent allogeneic HSCT for hematologic malignancies at Memorial Sloan Kettering Cancer Center (MSKCC) from January 1, 2005 until September 30, 2010. During this time, MSKCC was a 432-bed tertiary care facility in New York City with 19,000 annual admissions and 140,000 patient days. The adult bone marrow transplant unit at MSKCC is composed of a 29-bed unit, whereas the pediatric inpatient unit has 39 beds. All allogeneic HSCT patients are admitted to a private room and routinely placed under protective isolation (mask and gloves).

All demographic, clinical, and laboratory information were obtained from the institutional Clinical Research Database. Additional information not available in this database was obtained by MD chart review. The MSKCC Institutional Review Board reviewed the study and granted a HIPAA waiver of authorization.

Antibacterial Prophylaxis

Patients received antibacterial prophylaxis starting from day −2 of allogeneic HSCT until development of febrile neutropenia, overt infection, or engraftment, whichever occurred first. The choice of agent was levofloxacin for patients receiving a nonmyeloablative conditioning regimen regardless of stem cell source. Ciprofloxacin was used for cord blood recipients who underwent myeloablative or reduced-intensity conditioning. Vancomycin prophylaxis was used for recipients of peripheral blood or bone marrow allografts who received a myeloablative or reduced-intensity conditioning regimen. Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count >500 cells/μL. Fever was defined as a temperature ≥38.0°C.

Graft-versus-Host Disease

GVHD was monitored and managed as per MSKCC guidelines and was graded according to the International Bone Marrow Transplant Registry classification [16]. Acute lower GI GVHD was defined as GVHD that was diagnosed within the first 100 days after transplant.

Clostridium difficile Infection

Case definition

A case of CDI was defined by clinical history compatible with CDI and a positive test. "Early" CDI was an infection that occurred from day −10 until day +40 of transplant. This timeline was derived from the median length of stay for first transplants during the study period. Complicated CDI was defined by severe disease characterized by any of the following: systemic sepsis, intensive care unit admission, endoscopic evidence of pseudomembranous colitis, or toxic megacolon.

Diagnostic methods

From January 2005 until September 2008, diagnosis of CDI at MSKCC was performed by the cytotoxin neutralization assay. After September 2008, a 2-step testing algorithm was implemented that included a first-step glutamate dehydrogenase assay followed by the cytotoxin neutralization assay for all glutamate dehydrogenase–positive samples. *C. difficile* isolates were routinely stored for typing only after January 2008. PCR ribotyping and multilocus sequence typing (MLST) of isolates was performed as previously described [17,18].

Treatment for CDI

First-line treatment was metronidazole 500 mg p.o. (or i.v. for patients unable to tolerate oral medications) every 8 hours for a total of 14 days or discontinuation of broad-spectrum antibiotics, whichever was longer. Second-line treatment was oral vancomycin 125 mg p.o. 4 times daily at the discretion of the treating physician.

Statistical Analysis

Incidence rates were calculated by using the number of events divided by the total number of patient-days at risk. All second transplants were removed from the numerator and denominator when calculating incidence. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Mann-Whitney rank sum test for the baseline characteristics of early CDI. Simple logistic regression was used for the univariate analysis of risk factors of early CDI. Multiple logistic regression was used for multivariate analysis of risk factors of early CDI among adult patients.

Time-to-event analyses were conducted by Kaplan-Meier methods and log-rank test. Competing events for developing GVHD included patient death, relapse, and second transplant. Patient-days at risk for acute lower GI GVHD were from day 0 of transplant until the development of acute GVHD of the lower GI tract (stage ≥ 2), day +100 of transplant, second transplant, or death, whichever occurred first. $P < .05$ was considered to be statistically significant. All statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 793 allogeneic HSCTs were performed during the study period, comprising 598 adult patients and 195 pediatric patients. Overall, 169 patients (21.3%) had at least 1 episode of CDI in the first year after transplant. Early CDI occurred in 94 transplant recipients (11.9%), including 25 patients younger than 21 years. Overall, the incidence of early CDI was 25.2 cases per 10,000 patient-days at risk. The highest percentage of cases were observed in the years 2007 and 2008 (14.3 and 16.3%, respectively) and declined subsequently to 9.1% in 2010 ($P = .38$). No outbreaks were reported during the study period (Figure 1).

C. difficile Characteristics and Outcome

Ninety-four patients had early CDI, and 56% of infections occurred from day −5 to day +5 (Figure 2). Table 1 shows the baseline characteristics of the study cohort, and Supplementary Table 1 shows clinical characteristics of patients with early CDI. Diarrhea was mild (grade 1) in most cases (76.1%). Forty-four percent of patients were neutropenic, and none developed acute renal failure at the time of CDI. Fourteen patients had imaging with abdominal x-ray series or computed tomographic scanning; 3 among these had evidence of colitis and none had ileus, toxic megacolon, or evidence of perforation. There were no deaths attributed to CDI.

Most patients received metronidazole (91/94) at a dose of 500 mg 3 times daily for 10 to 14 days or until an alternate agent was used. For 8 of 91 patients, treatment was changed to vancomycin because of persistent diarrhea (median time to treatment switch, 5.5 days; range, 3 to 8 days). The time of onset of CDI for all but 1 case with refractory diarrhea was between day −7 and day 0. Seven of these patients had persistent diarrhea despite changing to vancomycin, and antimotility agents were eventually used for symptom relief. In 4 of 7 cases, retesting for CDI was done before initiating antimotility agents and was negative in all cases. For 1 patient, diarrhea resolved after changing to vancomycin without concomitant use of antimotility agents. Molecular typing was done on isolates retrieved from 7 of 8 patients; none was infected with the NAP1/027 strain.

Concomitant antibacterial agents for fever and neutropenia prophylaxis or management of concurrent infection were used in 89% of patients during CDI treatment (Table 2). Twenty-nine patients (31%) had relapse of CDI. The median time to relapse was 79 days. Nine patients (9.6%) had early relapse within 8 weeks after the index episode.