Biol Blood Marrow Transplant 22 (2016) 2243–2249

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Clinical Research: Supportive Care

Decline in the Use of Surgical Biopsy for Diagnosis of Pulmonary Disease in Hematopoietic Cell Transplantation Recipients in an Era of Improved Diagnostics and Empirical Therapy

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Article history:
Received 14 May 2016
Accepted 22 August 2016

Key Words:
Late pulmonary complications
Surgical lung biopsy
Aspergillosis
Bronchoscopy
Post-transplant

A B S T R A C T

Historically, diagnosis of enigmatic pulmonary disease after hematopoietic cell transplantation (HCT) required lung biopsy, but recent advancements in diagnosis and therapy for respiratory infections have changed how clinicians approach pulmonary abnormalities. We examined temporal trends in the use of lung biopsy after HCT. We retrospectively reviewed patients who underwent their first allogeneic HCT at the Fred Hutchinson Cancer Research Center between the years 1993 to 1997, 2003 to 2007, and 2013 to 2015 and subsequently underwent surgical lung biopsy for any reason. Lung biopsy between cohorts were analyzed using a Cox proportional hazards model with death and relapse considered competing risks. Of 1418 patients, 52 (3.7%) underwent 54 post-HCT surgical lung biopsies during 1993 to 1997 compared with 24 (2.1%) and 25 biopsies in the 2003 to 2007 cohort; 2 cases of surgical lung biopsies out of 786 HCT recipients occurred during the 2013 to 2015 cohort (.25%). The median time to biopsy post-HCT was 71.5 days (IQR, 31 to 89) for the early cohort and 97 days (IQR, 42 to 124) for the late cohort, for an overall biopsy incidence of .15 and .075 per 1000 patient days in the first year after HCT, respectively. Patients in the 2003 to 2007 cohort were less likely to undergo a lung biopsy (adjusted HR, .50; 95% CI, .29 to .83; $P = .008$) when compared with patients in the early cohort, but more patients in the early cohort underwent lung biopsy without antecedent bronchoscopy (25/54 [46%] versus 3/25 [12%], $P = .005$). Although infections were a more common finding at biopsy in the early cohort (35/1418 versus 8/1148, $P < .001$), the number of biopsies demonstrating noninfectious lesions was similar between the two cohorts (19/1418 versus 17/1148, $P = .76$). Fungal infections were the major infectious etiology in both cohorts (32/35 [91%] versus 5/8 [63%], $P = .07$), but there was a significant reduction in the number of *Aspergillus* species found at biopsy between the cohorts (30/54 versus 1/25, $P < .001$). A similar percentage underwent biopsy with therapeutic intent for invasive fungal disease in the 2 cohorts (8/54 [15%] versus 4/25 [16%]). Surgical evaluation of lung disease in HCT recipients significantly declined over a span of 2 decades. The decline from the years 1993 to 1997 compared with 2003 to 2007 was because of a reduction in the number of biopsies for post-transplant infections due to aspergillosis, which is temporally related to improved diagnostic testing by minimally invasive means and the increased use of empiric therapy with extended-spectrum azoles. This practice of primary nonsurgical diagnostic and treatment approaches to pulmonary disease post-HCT have continued, shown by low numbers of surgical biopsies over the last 3 years.

INTRODUCTION

Pulmonary complications are frequently encountered in patients undergoing hematopoietic cell transplantation (HCT) and are due to a variety of infectious and noninfectious etiologies, many of which are indistinguishable by either

Financial disclosure: See Acknowledgments on page 2248.

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http://dx.doi.org/10.1016/j.bbmt.2016.08.023
1083-8791/

symptoms or radiologic imaging. Because treatment options vary widely, misdiagnosis can lead to inappropriate therapy, compromise recovery, and lead to excess morbidity and mortality. An aggressive diagnostic approach is essential for the accurate identification of pulmonary complications in these high-risk patients.

Historically, the diagnostic approach of enigmatic lung disease after HCT often led to surgical lung biopsy [1,2]. Surgical lung biopsy has the advantage of being diagnostic as well as therapeutic in some instances, particularly in focally invasive fungal infection. However, improved noninvasive diagnostic modalities for infections have allowed for early diagnosis and detection by less invasive fiberoptic bronchoscopy, thus obviating the need for surgery [3-5]. The emergence of broad-spectrum triazole antifungals and liposomal–lipid complex polyenes in the early 2000s [6,7] have allowed for increased use of less toxic empiric therapy for patients with presumed fungal infections, further limiting the necessity of antecedent lung biopsy. Still, in many situations in which the diagnosis remains uncertain, lung biopsy remains the gold standard for achieving a diagnosis.

The purpose of this study was to examine the temporal trends in the use of surgical lung biopsy in HCT patients as it relates to the emergence of improved diagnostic and therapeutic strategies of invasive fungal disease. In addition, we examined the diagnostic outcomes and the utility of lung biopsy in relationship to bronchoscopy when considering the time period before the routine use more efficacious broad-spectrum triazole antifungal regimens. Finally, we propose a potential strategy for diagnostic workup and decision-making for appropriate use of surgical lung biopsy in HCT.

METHODS

Patients

We reviewed data on patients who received their first allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC) between the years 1993 to 1997 (early cohort) and 2003 to 2007 (late cohort). A third cohort for the years 2013 to 2015 (current cohort) was also reviewed. Recipients who underwent surgical lung biopsy within 1 year (365 days) of HCT were identified from a prospectively collected database of all allogeneic transplant patients as previously described [8]. Additional cases were also identified through pathology records and confirmed by chart review. Cases with incomplete clinical or biopsy data from other institutions were excluded from analysis. The study protocol was approved by the institutional review board of the FHCRC.

Transplant Procedures

Patients received a conditioning regimen followed by infusion of donor cells as determined by the transplant team. After transplant, all patients received immunosuppressive agents as prophylaxis against graft-versus-host disease in the post-transplant period. Standard infectious prophylaxis included acyclovir for herpes simplex virus and or varicella zoster virus; trimethoprim-sulfamethoxazole, atavoquone, or dapsone for *Pneumocystis jirovecii*; and fungal prophylaxis with fluconazole [9]. All patients received either ceftazidime or levofloxacin for neutropenic prophylaxis [10]. In the later cohort, patients with proven or probable fungal infections [11] or those with pulmonary nodules were more likely to get extended-spectrum azoles (voriconazole and posaconazole). Patients with cytomegalovirus (CMV) infection (on the basis of antigen or DNA testing) were given preemptive therapy with ganciclovir or foscarnet [12].

Pulmonary Evaluation

Patients who developed respiratory symptoms after HCT underwent diagnostic tests including imaging studies (chest radiograph and/or computed tomography of the chest) and laboratory testing, and empiric treatment was ordered at the discretion of the primary service. Subsequent decisions for invasive diagnostic workup, including bronchoaveolar lavage (BAL), fine needle aspiration (FNA), and/or surgical lung biopsy, were made in consultation with the pulmonary, infectious diseases, and thoracic surgery services. If a BAL was performed, all samples were tested for evidence of specific pathogens as listed in Table 1; all specimens also underwent cytopathologic review by a pathologist at the center.

Table 1
Diagnostic Tests Performed on BAL Fluid

Category	Specific Test	Available in 1993-1997	Available in 2003-2007*
Bacterial	Gram stain and culture	+	+
	Acid fast	+	+
	Modified acid fast	+	+
	Modified Gimenez stain	+	+
	Legionella culture	+	+
	Nocardia culture	+	+
	Actinomycoses culture	+	+
Fungal	Giemsa silver stain	+	+
	Pneumocystis DFA	+	+
	Fungal stain and culture	+	+
	Galactomannan	-	+
	Fungal PCR	-	+
Viral	Routine viral culture	+	+
	CMV shell vial	+	+
	CMV rapid DFA	-	+
	Influenza rapid DFA	-	+
	Other human herpesvirus DFAs†	+	-
	Other human herpesvirus PCRs†	-	+
	Respiratory virus PCRs‡	-	+
Other	Periodic acid Schiff stain	+	+
	Cell count and differential	+	+
	Cytologic review	+	+

DFA indicates direct fluorescent antibody.
* The 2013-2015 cohort had similar diagnostic tests performed.
† Includes HSV and HHV-6.
‡ Includes influenza A and B, parainfluenza (1-4), respiratory syncytial virus, human metapneumovirus, bocavirus, coronaviruses, rhinovirus, and adenovirus [4].

Definitions

Pathologic diagnoses were categorized into 3 main categories: infectious, noninfectious, and nondiagnostic. Biopsies were considered nondiagnostic if pathologic findings were nonspecific or if samples were insufficient for diagnosis. Antecedent bronchoscopy with BAL was defined as a bronchoscopy that was performed intentionally for the diagnosis of a pulmonary condition that was ultimately diagnosed or treated by surgical biopsy, before the surgical biopsy. Radiology reports were categorized by specific findings as seen on computed tomography modified from previously published definitions [2,13,14]: focal lesions, which included solitary pulmonary nodule, mass, or consolidation; multifocal infiltrates, masses, or consolidations; and 3) diffuse, which included diffuse ground glass opacities and/or nodular ground glass opacities with >50% of lung involved.

Statistical Analysis

Outcome data were analyzed using Fisher's exact test for categorical variables and Wilcoxon rank-sum for continuous variables. Incidence of surgical biopsy was calculated as the number of biopsies performed per cohort per total number of patient days at risk within 1 year. The cause-specific hazards for lung biopsy within 1 year were compared between the cohorts using a Cox proportional hazards model, where death and relapse were considered competing risks, and adjusted for patient age, severity of disease (low, intermediate, high), and donor type. The statistical software used was SAS, version 9.2 (SAS Institute, Cary, NC).

RESULTS

During 1993 to 1997 (early cohort), 102 chart-verified lung biopsies were performed on 1418 first allogeneic HCT recipients at FHCRC, of which 66 biopsies occurred post-HCT and comprised 54 surgical lung biopsies and 12 FNA among 56 patients. During 2003 to 2007 (late cohort), 56 lung biopsies were performed, including 32 post-HCT biopsies (25 surgical, 7 FNA) in 28 patients. There was 1 pre-HCT transbronchial biopsy in both the 1993 to 1997 and the 2003 to 2007 cohorts but no post-HCT transbronchial biopsies. There were 2 post-HCT surgical lung biopsies and 2 FNA in 4 patients in the current cohort (2013 to 2015). Most surgical biopsies were performed thoracoscopically: 33 of 54 (61%), 19 of 25 (76%), and 2 of 2 (100%) in the early, late, and current cohorts, respectively.