Biol Blood Marrow Transplant 20 (2014) 1229–1237

A Comparison of Bronchoalveolar Lavage versus Lung Biopsy in Pediatric Recipients after Stem Cell Transplantation

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Article history:
Received 7 February 2014
Accepted 17 April 2014

Key Words:
Bronchalveolar lavage
Lung biopsy
Pediatrics
Stem cell transplantation

A B S T R A C T

Bronchoalveolar lavage (BAL) has been a useful initial diagnostic tool in the evaluation of pulmonary complications after hematopoietic stem cell transplantation (HSCT); however, the diagnostic sensitivity, prevalence, and outcome after BAL versus lung biopsy (LB) in pediatric HSCT patients remains to be determined. We reviewed 193 pediatric HSCT recipients who underwent a total of 235 HSCTs. Sixty-five patients (34%) underwent a total of 101 BALs for fever, respiratory distress, and/or pulmonary infiltrates on chest radiograph and/or computed tomography scan. The 1-year probability of undergoing BAL was 43.0% after allogeneic stem cell transplantation (alloSCT) and 8.5% after autologous stem cell transplantation (autoSCT) ($P = .001$). Sixteen of the 193 patients (8%) patients underwent 19 LBs. The probability of undergoing LB at 1 year after HSCT was 9.3%. No grade III or IV adverse events related to either procedure were observed. Of the 101 BALs performed, 40% (n = 40) were diagnostic, with a majority revealing a bacterial pathogen. Among the 19 LBs performed, 94% identified an etiology. In multivariate analysis, myeloablative conditioning alloSCT conferred the highest risk of requiring a BAL (hazard ratio [HR],8.5; $P = .0002$). The probability of 2-year overall survival was 20.2% in patients who underwent BAL, 17.5% for patients who underwent biopsy, and 67.4% for patients who had neither procedure. In multivariate analysis, only the requirement of a BAL was independently associated with an increased risk of mortality (HR, 2.96; $P < .0001$). In summary, in this cohort of pediatric HSCT recipients, BAL and LB were used in approximately 35% and 8% of pediatric HSCTs with diagnostic yields of approximately 40% and 94%, respectively, and were both associated with poor long-term outcomes.

INTRODUCTION

Pulmonary complications have been reported in approximately 25% of pediatric recipients after hematopoietic stem cell transplantation (HSCT) [1]. Infectious etiologies are the most prevalent causes of pulmonary dysfunction after HSCT [2]. Early pulmonary complications have been associated with a significantly decreased overall survival in children after allogeneic HSCT (alloSCT) [3]. HSCT recipients who present with clinical and radiological findings of pulmonary infiltrates often receive empiric broad-spectrum antimicrobial therapy [4]. However, a delay in establishing a definitive diagnosis has been shown to be a negative prognostic factor in immunocompromised patients [4,5]. To establish an earlier, more definitive diagnosis, bronchoalveolar lavage (BAL) is regarded as an initial diagnostic tool in pediatric immunocompromised patients with pulmonary dysfunction [6]. However, the diagnostic yield of BAL in pediatric HSCT recipients has been reported as varying from 29% to 68%, with a reduced yield in those patients with grade II to IV graft-versus-host disease (GVHD) and in those receiving immunosuppressive therapy [7,8]. It has been suggested that some of this variation could result from the procedure's timing, with higher diagnostic yield and favorable impact on survival resulting from early use of BAL, but this requires further investigation [9].

In the absence of definitive findings from BAL, many patients continue to receive empiric antimicrobial treatments that can have deleterious toxicities, including but not limited to ototoxicity, renal insufficiency, and hepatotoxicity [10,11].

Financial disclosure: See Acknowledgments on page 1236.

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1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.04.019

Furthermore, radiographic findings of pulmonary infiltrates in HSCT recipients may indicate noninfectious processes, including GVHD, disease recurrence, and treatment/transplantation-associated toxicity [12].

After HSCT, children are also at risk for a variety of noninfectious pulmonary complications, which are unlikely to be diagnosed after a BAL, including GVHD, idiopathic pneumonia syndrome, and interstitial fibrosis [13-15]. Lung biopsy (LB) can have an increased diagnostic yield, given its ability to detect infectious and noninfectious etiologies. The diagnostic sensitivity of LB has been reported to be 60% to 100% in patients with pulmonary complications after HSCT [13-15]. However, diagnosis based on LB specimens has been reported to be less sensitive in immunocompromised children [14,16-18]. Additionally, the reported complication rates in children after open LB (OLB) vary widely, from 2% to 52%, depending on the patients' underlying disease and degree of immunocompromise [17].

The impact of LB on overall survival has not yet been prospectively evaluated. In retrospective studies of pediatric populations, LB led to a specific diagnosis in most cases, with the most common organisms recovered being cytomegalovirus (CMV) and *Aspergillus fumigatus*; the overall mortality after LB ranged from 24% to 45% [13-15]. Single-institution experience demonstrated that OLB was very effective at identifying pulmonary pathology in pediatric HSCT recipients but had little impact on mortality. OLB identified noninfectious causes in 58% of the cases and an infectious organism in 30% of cases; postoperative complications were reported in 47% of patients [9].

Reduced-toxicity conditioning (RTC) has recently been employed in children before allogeneic HSCT, as we have previously reported [19-23]. Although this approach may reduce early mortality, there seems to be similar risk of viral and fungal infections compared with those receiving myeloablative conditioning (MAC) [21]. However, there have been no reported studies that evaluated the impact of pulmonary complications comparing MAC or RTC in pediatric HSCT recipients. Furthermore, there is a paucity of information reporting the safety and effectiveness of video-assisted thoracoscopy (VAT) or computed tomography (CT)–guided biopsy in pediatric HSCT recipients. Therefore, in the current study, we examined the diagnostic yield of BAL and LB, including OLB, VATs, and CT-guided biopsies, and also compared the survival of children with pulmonary complications after autologous and allogeneic HSCT with either prior RTC or MAC.

METHODS

Patients

We evaluated the safety and efficacy of BAL and LB in 193 consecutive children and adolescents who underwent HSCT at New York-Presbyterian Morgan Stanley Children's Hospital. Patients received MAC or RTC before allogeneic transplantation (MAC alloSCT, RTC alloSCT) or MAC before autologous transplantation (MAC autoSCT). All patients were enrolled on institutional review board–approved research protocols and parents and/or patients signed informed consent, as applicable, before to the initiation of therapy. All research was conducted in compliance with the Declaration of Helsinki. The following studies were registered with clinicaltrials.gov: NCT00669890, NCT01050439, NCT00802113, NCT00408447. This retrospective study was approved by the institutional review board of Columbia University Medical Center.

Conditioning Regimens

Conditioning regimens were largely protocol driven and disease specific, and they consisted of both MAC (n = 172, 63%) and RTC (n = 72, 37%). Most MAC regimens consisted of total body irradiation (TBI, 1200 cGy) or busulfan (12.8 mg/kg in patients > 4 years of age, 16 mg/kg in patients ≤ 4 years of age) in combination with melphalan (135 mg/m^2) or cyclophosphamide as follows: TBI/melphalan, TBI/cyclophosphamide, busulfan/cyclophosphamide, or busulfan/melphalan. Lung shielding was not used for TBI-containing regimens. Busulfan-containing conditioning regimens utilized busulfan pharmacokinetic dose adjustment and were targeted to achieve 600 to 900 ng/mL steady-state concentration, as we have previously reported [20,23]. RTC regimens were fludarabine-based (150 to 180 mg/m^2) as follows: fludarabine/busulfan (12.8 mg/kg in patients > 4 years of age, 16 mg/kg in patients ≤ 4 years of age) and fludarabine/cyclophosphamide, as we have previously reported [23]. Many patients also received rabbit antithymocyte globulin or alemtuzumab as part of RTC prior to AlloSCT [19].

Cell Sources, HLA Typing, and Donor Chimerism Studies

Grafts were from unrelated and related donors, with cell sources of bone marrow, peripheral blood stem cells, or cord blood. HLA typing was performed, and transplantations were classified as fully matched or HLA-mismatched with 1 or 2 differences, as we previously described [19,24,25].

GVHD Prophylaxis

Acute GVHD (aGVHD) prophylaxis consisted of tacrolimus and mycophenolate mofetil (MMF). Tacrolimus was administered starting at .03 mg/kg per day as continuous i.v. infusion or .12 mg/kg orally (PO) twice a day, with dosage adjustment to maintain blood levels between 5 and 20 ng/mL, starting on the first day of conditioning regimen or 1 day before transplantation (day −1), as we have previously reported [26,27]. MMF was administered at 15 to 30 mg/kg every 6 to 12 hours, either PO or i.v., starting the day after transplantation (day +1), as we have previously described [26,27]. For sibling donor transplant recipients, at day +30, MMF was stopped and tacrolimus was weaned over a 4 to 8 week period if patients had ≤ grade II aGVHD. For unrelated donor transplant recipients, MMF was stopped at day +30 and tacrolimus was continued until day +60, when it was weaned over a 4 to 8 week period, if patients had ≤ grade II aGVHD [26,27]. Acute GVHD and chronic GVHD (cGVHD) were graded according to Seattle consensus criteria [28]. All patients who achieved any level of donor chimerism were considered at risk for developing aGVHD. Only patients with sustained engraftment of donor hematopoiesis and surviving for more than 100 days after transplantation were evaluated for the development of cGVHD.

Supportive Care

Infectious disease prophylaxis consisted of the following: herpes simplex virus prophylaxis (from day −5 until neutrophil engraftment with acyclovir 250 mg/m^2/dose i.v., every 8 hours), antifungal prophylaxis from day 0 to day 100 with liposomal amphotericin B 3 mg/kg i.v. daily as we have previously reported [29], *Pneumocystis jirovecii* prophylaxis (beginning when absolute neutrophil count (ANC) ≥ 500/mm^3 × 2 days after transplantation) with trimethoprim sulfamethoxazole (TMP/SMX) 5 mg/kg/day PO divided twice daily thrice weekly or pentamidine 4 mg/kg i.v. every 2 weeks for patients unable to tolerate TMP/SMX, and cytomegalovirus (CMV) prophylaxis (when ANC ≥ 750/mm^3 × 2 days after transplantation and donor and/or recipient were CMV+) with foscarnet 90 mg/kg i.v. every other day, alternating with ganciclovir 5 mg/kg i.v. every other day until day 100, as we have previously reported [30]. All patients received sargramostim (250 μg/m^2 per day) i.v. daily from day 0 until the white blood cell count reached ≥ .3 × 10^9/L for 2 days and then were switched to filgrastim (10 μg/kg per day) either i.v. or subcutaneously until an ANC ≥ 2.5 × 10^9/L was achieved for 3 days, as we previously described [31]. Intravenous immune globulin (IVIG) 200 mg/kg was administered starting on day −1 and continued every 3 weeks until day +100. IVIG was discontinued on day +100 for patients with < grade II aGVHD. For patients with ≥ grade II aGVHD on day +100, treatment was continued until the severity of aGVHD was < grade II. Patients with IgA deficiency were given IVIG products low in IgA. Patients who developed cGVHD or relapse of greater than or equal to grade II aGVHD resumed IVIG prophylaxis until severity of aGVHD was less than grade II.

BAL and Biopsy Procedures

BAL was performed by a pediatric pulmonologist, using an age-adjusted flexible bronchoscope. Warmed sterile normal saline was instilled in 4 to 6 aliquots of 10 to 20 cc, which was suctioned and sent for pathology and microbiology evaluation.

LBs were by VATS, OLB, or CT-guided biopsies, at the discretion of the pediatric HSCT physician and pediatric surgeon. OLBs and VATS were performed by a pediatric surgeon. Further intervention or resection was at the discretion of the surgeon. CT-guided biopsies were performed by an interventional radiologist, obtaining fine needle aspiration and core biopsy samples.