Fiberoptic Bronchoscopy and Bronchoalveolar Lavage for the Evaluation of Pulmonary Infiltrates after BMT in Children.

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Summary.

Thirty-one fiberoptic bronchoscopies and BAL performed within 4 days after the appeareance of pulmonary infiltrates in 28 children who received BMT were reviewed. A causative agent was identified in 67% of patients with diffuse infiltrates (*Cytomegalovirus* in 8 cases, *Pneumocystis carinii* in 4) and in 31% of those with localized infiltrates (*Aspergillus* in 2, bacteria in 2). No relevant side effect was reported. The results obtained from cytological and microbiological testing provided relevant informations for the management of most cases, regardless to the identification of a specific pathogen. We conclude that BAL is a safe diagnostic procedure that should be considered early after the onset of pulmonary complications in BMT recipients.

Pulmonary complications are a very frequent cause of morbidity and mortality after bone marrow transplantation (BMT), so as one of the greatest clinical challenge in the management of these immunecompromised patients is the diagnosis and the treatment of new lung infiltrates.[1] The etiology of pulmunary complications in BMT recipients may include infections, hemorrage, drug or radiation toxicity, GvHD, heart failure, embolism and increased capillary permeability. Due to the wide range of etiologic factors and of their possible coexistance, a precise diagnosis of pulmonary diseases is generally difficult on the basis of the so-called pattern recognition of pulmonary infiltrates.[2] Fiberoptic bronchoscopy with broncho-alveolar lavage (BAL) has been proposed as a safe and sensitive technique in the diagnosis of lung infiltrates in this group of patients, in whom the speed of clinical assessment and, therefore, of the institution of an appropriate treatment is critically related to survival.[3,4] BAL has been extensively used first in adults, but the advent of small diameter instruments has given the opportunity to extend the procedure to small children.[5,6,7] The purpose of this analysis is to evaluate a single institution series of 31 BALs performed over a 6-year period in a pediatric population of BMT recipients.

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Patients and Methods.

Medical records of 187 consecutive patients with hematological, oncological or congenital disorders who underwent BMT at Giannina Gaslini Children's Research Institute from 1990 to February 1996 were reviewed to evaluate data concerning fiberoptic

bronchoscopy and BAL. Thirty-tree children were transplanted twice (allogeneic 5, autologous 28), thus increasing the total number of transplants to 220 (allogeneic 79, autologous 141). The median age of patients was 6 years (range 1-16) and the male/female ratio 1.52.

Fiberoptic bronchoscopy and BAL was considered as an indication at any time after BMT in the presence of roentgenographic evidence of pulmonary infiltrates not related to fluid overload and was performed after the obtention of an informed consent by parents. Subsequent BALs performed during the follow-up of the same pulmonary episode or for routine surveillance of Cytomegalovirus (CMV) infection were excluded from this analysis.

Profoundly thrombocytopenic children were transfused to obtain counts above $50x10^9$/L. The Olympus BF, 3C 20, flexible pediatric fibrobronchoscopy was inserted into the tracheobronchial tree either trough the nose or an endotracheal tube, depending on the place where the procedure was performed (i.e. at bedside with mild sedation and local anesthesia or in the operative room under general anesthesia). In patients with diffuse lung infiltrates, BAL was performed in the right middle lobe. Sterile isotonic saline solution (0.5-1.0 ml/Kg of body weight for each of 3 to 5 different aliquots) was instilled and suctioned into sterile collection traps. The lavage was immediately processed for microbiological, virological and cytological testing by means of the techniques available at the time of any specific procedure.

Results

Twenty-eight children (median age 6 years; range 2-16) were investigated with BAL after BMT. Three patients were investigated twice, for the evaluation of different episodes of pneumonia. The median time elapsed between the diagnosis of pulmonary infiltrates and the procedure was 1 day (range 0-4 days), the median interval between the transplant and the BAL was 41 days (range 8-400). Among the 31 BALs included in this series, 21 were performed in recipients of allogeneic BMT, 10 in recipients of autologous BMT; overall, the frequency rate of BAL was 27% and 7% after allogeneic and autologous BMT, respectively ($p < .01$). (Table 1)

BAL was performed at bedside under cardiorespiratory monitoring, O_2 supplement and rescuscitation assistence with mild sedation and local anesthesia in 17 children (median age 13 years), in the operative room under general anesthesia in 12 children (median age 4 years), in the intensive care unit in the remaining 2 cases who were already under mechanical ventilation. If we exclude a transient increase in the breath rate and O_2 request, no relevant adverse effect has been reported. In 2 children with rapidly progressive

Table1. Characteristics of patients who underwent BMT and BAL between 1990-1996

	BMT	BAL	Frequency
N° of patients	**187**	**28**	**15%**
N° of procedures	**220**	**31**	**14%**
Median age, years (range)	**6 (1-16)**	**6 (2-16)**	**-**
Male/Female ratio	**1.5**	**1.9**	**-**
Allogeneic BMT	**79**	**21**	**27%**
Autologous BMT	**141**	**10**	**7%**

interstitial pneumonia, respiratory failure necessitating mechanical ventilation occurred within 12 hours from BAL.

According to the lung Xray pattern, pulmonary infiltrates were diffuse in 18 (58%) and localized in 13 (42%) children who underwent BAL. Overall, a causative pathogen was identified in 16/31 (52%) lavage specimens. In children with diffuse infiltrates, 12/18 (67%) BALs were diagnostic: CMV was detected in 8 cases (allo BMT 6, auto BMT 2), *Pneumocystis carinii* in 4 (allo BMT 2, auto BMT 2). In 2 children with CMV pneumonia, the lavage fluid grew also *Pseudomonas* spp. In children with localized infiltrates, 4/13 (31%) BALs, all obtained from recipients of allo BMT, were diagnostic; *Aspergillus* spp (2 cases), *Serratia* spp and *Staphylococcus* spp (1 case each) were isolated. The characteristics of patients with positive BAL and their outcome are listed in Table 2.

A complete regression lined of pulmonary infiltrates was obtained in 56% of patients for whom a causative pathogen was isolated. Seven children in this group progressed to lethal respiratory failure despite the institustion of a specific treatment; the pathogenesis was CMV in 3 cases, *Pneumocystis carinii* in 2 and *Aspergillus* spp. in 2. Among the 15 children with a negative BAL (diffuse infiltrate 6, localized infiltrate 9), pulmonary infiltrates resolved with broad spectrum empiric treatment in 12 cases, whereas respiratory failure progressed to death in 3. Post mortem evaluation was obtained in 2 of them and revealed lung GvHD and *Pseudomonas* spp pneumonia, respectively.

Conclusions

Pulmonary problems continue to be a major source of morbidity and mortality for recipients of allogeneic and, at a lesser degree, autologous bone marrow transplant. Fiberoptic bronchoscopy and BAL has been proven to be a safe and sensitive diagnostic procedure to evaluate lung infiltrates in this particular setting. Our experience confirms previous reports and demonstrates that BAL can be safely performed at bedside with resuscitation assistence in most cases and even in very young children. The probability to obtain a specific diagnosis was high in patients with diffuse infiltrates, whereas only one third of specimens obtained from the lavage fluid of patients with localized infiltrates was

Table 2. Characteristics of 16 patients with a diagnostic BAL and their outcome

UPN	Age at BAL	Type of BMT	Day of BAL	XRay pattern	Organism	Outcome
139	5	Allo UD	400	Diffuse	PC	Died
143	14	Allo UD	23	Diffuse	PC	Resolved
144	14	Allo UD	69	Diffuse	CMV	Resolved
156	16	Allo	97	Diffuse	CMV	Resolved
187	16	Allo	380	Localized	Staphylococcus	Resolved
193	13	Allo	300	Localized	Aspergillus	Died
201	13	Allo	21	Diffuse	CMV	Resolved
204	4	Allo	51	Localised	Serratia spp	Resolved
232	4	Allo UD	68	Diffuse	CMV	Resolved
234	5	Allo UD	83	Diffuse	CMV	Died
243	6	Auto	99	Diffuse	PC	Resolved
262	4	Auto	108	Diffuse	PC	Died
311	15	Allo UD	144	Localized	Aspergillus	Died
335	3	Allo UD	42	Diffuse	CMV	Died
357	2	Auto	14	Diffuse	CMV	Resolved
360	3	Auto	8	Diffuse	CMV	Resolved

Allo, allogeneic transplant; Auto, autologous transplant; UD, unrelated donor;
PC, Pneumocystis carinii

diagnostic. The procedure, however, provided relevant informations that guided therapy in most cases, including those in which it was nondiagnostic. A "negative" BAL , infact, rouled out in the differential diagnosis many etiologic factors, exspecially in patients with diffuse infiltrates, where viruses, *Pneumocystis carinii* and non-infectious factors are most likely to be involved in the pathological processes. The opportunity to perform BAL also in patients with early onset diffuse lung infiltrates was confirmed by 3 unusual cases reported in our series: 2 neuroblastoma patients who received autologous BMT were diagnosed with CMV pneumonia in the aplastic phase after transplant (day +8 and +14, respectively), and 1 CML patient, previously reported[8], was diagnosed with *Pneumocystis carinii* pneumonia on day +23 after unrelated donor BMT. Pneumonia resolved in all these patients after the institution of specific treatment.

For patients with localized infiltrates unresponsive to broad spectrum antibacterial-antifungal therapy and negative BAL, alternative and more invasive diagnostic measures, such as fine-needle aspiration or thoracotomy with biopsy, should probably be considered in selected cases.

In conclusion, our experience further support the suggestion that bronchoscopy and BAL is a safe procedure that should be performed as early as possible after the onset of respiratory problems in BMT recipients.

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