Effect on survival of the development of late-onset non-infectious pulmonary complications after stem cell transplantation

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We evaluated the incidence, risk factors, and clinical outcome of late-onset non-infectious pulmonary complications (LONIPC) in 599 patients who underwent hematopoietic allogeneic stem cell transplantation (HSCT). The 2-year cumulative incidence of LONIPC was 10% among the 438 patients surviving more than 3 months after HSCT. Transplants from an unrelated donor and occurrence of extensive chronic graft-versus-host disease were the variables significantly associated with the development of LONIPC. The 5-year overall survival was significantly worse among patients with LONIPC than among those without (34% vs 65%, p=0.009). Causes of death were respiratory failure and infections. The relapse rate was similar in the two groups.

Key words: late-onset non-infectious pulmonary complications, LONIPC, survival, stem cell transplantation.

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative procedure for a wide variety of hematologic diseases. However, despite improvement in supportive care, the risk of morbidity and mortality related to this procedure continues to be a major concern for physicians and patients. Pulmonary complications occur in 40-60% of patients undergoing HSCT, causing 10-40% of transplant-related deaths.[1] The spectrum of pulmonary complications includes infectious and non-infectious conditions. These are classified as early or late depending on whether they occur before or after 100 days post-transplantation. The term late onset non-infectious pulmonary complications (LONIPC) has been used as a generic name for different entities occurring later than 3 months after transplant, such as interstitial pneumonia (IP), bronchiolitis obliterans (BO), and bronchiolitis obliterans with organizing pneumonia (BOOP).[2] In this study we retrospectively evaluated the incidence and the clinical outcome of LONIPC in 599 patients who underwent HSCT in order to identify possible risk factors and determine the response to treatment.

Design and Methods

We retrospectively analyzed 599 patients who underwent allogeneic HSCT at the transplantation centers of the University Hospitals of Udine and Bologna between January 1992 and December 2004. The 438 patients who survived more than 3 months after transplantation were eligible for the study. The patient and transplant characteristics are shown in Table 1. The assessment and grading of acute and chronic graft-versus-host disease (GVHD) were primarily based on clinical findings and followed the commonly accepted diagnostic criteria.[3,4] Grading of chronic GVHD did not take in account the pulmonary involvement. Patients were clinically examined weekly during the first 3 months, every 2 weeks until 1 year after HSCT and monthly afterwards. Chest X-rays and high-resolution computed tomography (CT) were performed in case of respiratory symptoms or fever. Pulmonary function tests (PFT) were routinely performed a week before BMT and after 3, 6, 12 and 24 months or repeated on the basis of clinical indications. PFT were performed according to the American Thoracic Society guidelines.[5] A diagnosis of LONIPC was made in patients who developed symptoms and clinical or radiological signs of lung disease and/or abnormalities in PFT 3 months after transplantation without any evidence of an infectious cause. To exclude infection, standard culture and staining methods for bacterial, viral and protozoan pathogens were employed. Bronchoalveolar lavage, transbronchial lung biopsy or CT-guided lung biopsy were performed whenever possible or necessary for diagnosis. Once a patient was identified as having LONIPC, a further classification was made on the basis of clinical, radiological, PFT and histologic findings. Patients were classified as having BO if they showed FVC percentage predicted ≥80% and FEV1/FVC <70%. A CT-scan showing

Table 1. Clinical characteristics of 438 patients surviving more than 3 months after HSCT.

Clinical characteristics	*No. of patients with LONIPC (%) total n=41*	*No. of patients without LONIPC (%) total n=397*
Age at HSCT (years) median (range)	37 (16-61)	39 (14-65)
Sex		
male	27 (66)	234 (59)
female	14 (34)	163 (41)
Diagnosis		
acute lymphoblastic leukemia	6 (15)	51 (13)
acute myeloid leukemia	14 (34)	100 (25)
chronic myeloid leukemia	9 (22)	103 (26)
multiple myeloma	5 (12)	71 (18)
chronic lymphoid leukemia	0 (0)	10 (2.5)
lymphoma	6 (15)	44 (11)
myelodisplastic syndrome	0 (0)	10 (2.5)
aplastic anemia-idiopathic myelofibrosis	1 (2)	8 (2)
Phase		
early	12 (29)	213 (54)
late	29 (71)	184 (46)
Donor		
Matched unrelated donor	22 (54)	110 (28)
Matched related donor	19 (46)	287 (72)
Source		
bone marrow	23 (56)	187 (47)
peripheral blood	18 (44)	210 (53)
Conditioning intensity		
conventional	37 (90)	329 (83)
reduced intensity	4 (10)	68 (17)
Conditioning regimen		
chemotherapy based	22 (54)	263 (66)
total body irradiation based	19 (46)	134 (34)
GVHD prophylaxis		
cyclosporine A+methotrexate	38 (93)	370 (93)
cyclosporine A+mycophenolate mofetil	2 (5)	23 (6)
campath	1 (2)	4 (1)
Anti-human T-lymphocytye rabbit serum		
yes	11 (27)	98 (25)
no	30 (73)	299 (75)
Acute GVHD		
grade ≥II	18 (44)	96 (24)
grade III-IV	5 (28)	35 (37)

HSCT: hematopoietic stem cell transplantation.

patchy or diffuse infiltrates associated with negative cultures of bronchoalveolar lavage fluid and, whenever available, with consistent histological findings were required to classify patients as having BOOP or IP. Response to therapy was defined as complete if there were no clinical and radiological signs of LONIPC and PFT normalized or showed an improvement of more than 50%. Patients without any improvement or with progression of signs of LONIPC were defined as non-responsive. The response was defined as partial in the remaining cases.

The occurrence of LONIPC was estimated by cumulative incidence rates. Overall survival was calculated by the Kaplan-Meier method; comparisons between probabilities in different patient groups were performed using the log-rank test. A Cox proportional hazard regression model was used for multivariate analysis of predictor variables for LONIPC. Variables found to be statistically significant ($p<0.05$) in univariate analysis were tested in multivariate analysis. The χ^2 test was used to compare differences in percentages, and the Mann-Whitney U test was used to compare continuous values. All p values were two-sided and p values <0.05 were considered statistically significant.

Results and Discussion

Of the 438 patients surviving more than 3 months after HSCT, 41 (9.4%) fulfilled the diagnostic criteria for LONIPC. The median time to diagnosis of LONIPC was 10 months after transplantation (range, 4-24) and 4 months after the onset of chronic GVHD (range, 0-13). The 2-year cumulative incidence of LONIPC was 10% (95% CI, 7.4-13.3) in all transplanted patients and 15.6% (95% CI, 11.7-20.7%) in those with chronic GVHD. All patients developed chronic GVHD before the diagnosis of LONIPC. The GVHD was progressive or quiescent in 20 cases (58%) and extensive in 35 cases (85%). The 41 patients with LONIPC were further subclassified as having BO (16 patients, 39%), BOOP (13 patients, 32%), and IP (12 patients, 29%). The diagnosis of BO was mainly based on the obstructive pattern of PFT. The 13 patients with BOOP had abnormal PFT, with a mixed pattern in six cases (46%) and with a mixed, mainly obstructive, pattern in seven cases (54%). High resolution CT of all patients with BOOP showed patchy infiltrates or opacities. The diagnosis of BOOP was supported in six patients by histological data obtained by CT-guided lung biopsy (2 patients), by transbronchial lung biopsy (2 patients) or after autopsy (2 patients) and in eight patients by negative bronchoalveolar lavage. The 12 patients with IP had bilateral diffuse (alveolar and interstitial) infiltrates on high resolution CT, abnormal PFT with a restrictive pattern in nine cases (75%) and with a mixed, mainly restrictive, pattern in three cases (25%). The diagnosis of IP was confirmed in four patients by histological data obtained by CT-guided lung biopsy (3 patients) or after autopsy (1 patient) and in eight patients by negative bronchoalveolar lavage. BOOP developed earlier after HSCT (7 months, range, 4-18) than did IP (11 months, range 4-20; $p=0.05$) or BO (12 months, range 4-24; $p=0.03$). The results of univariate analysis are shown in Table 2. An unrelated donor (HR 3.2, 95% CI 1.3-7.9; $p=0.01$) and extensive chronic GVHD (HR 5.9, 95% CI 2.4-14.6; $p=0.0001$) were the variables significantly associated with the development of LONIPC in multi-

Table 2. Univariate analysis of possible predictors of LONIPC.

Variables HR (95% CI)	*at time of cGVHD* value	*p*
Age at HSCT (years)		
> 29	0.6 (0.3-1.3)	0.2
≤29	1	
Sex		
male	1.5 (0.7-3.2)	0.3
female	1	
Diagnosis		
acute lymphoblastic leukemia	0.8 (0.2-2.5)	0.7
acute myeloid leukemia	2.7 (1.3-5.4)	0.006
chronic myeloid leukemia	0.8 (0.4-1.8)	0.6
multiple myeloma	0.4 (0.1-1.5)	0.2
chronic lymphoid leukemia-lymphoma	0.9 (0.4-2.5)	0.9
Phase		
late	2.3 (1.1-4.7)	0.02
early	1	
Donor		
matched unrelated donor	3.8 (1.9-7.7)	0.0002
matched related donor	1	
Source		
peripheral blood	0.6 (0.3-1.3)	0.2
bone marrow	1	
Conditioning intensity		
conventional	6.9 (0.9-50.8)	0.06
reduced intensity	1	
Conditioning regimen		
total body irradiaton based	2.5 (1.2-4.9)	0.01
chemotherapy based	1	
ATG		
no	0.6 (0.3-1.5)	0.3
yes	1	
Acute GVHD ≥2		
yes	1.9 (0.9-3.7)	0.07
no	1	
Grade of chronic GVHD		
extensive	5.8 (2.4-14)	0.0001
limited	1	
Onset-type of chronic GVHD		
progressive/quiescent	2.0 (0.9-4.2)	0.08
de novo	1	

HSCT: hematopoietic stem cell transplantation.

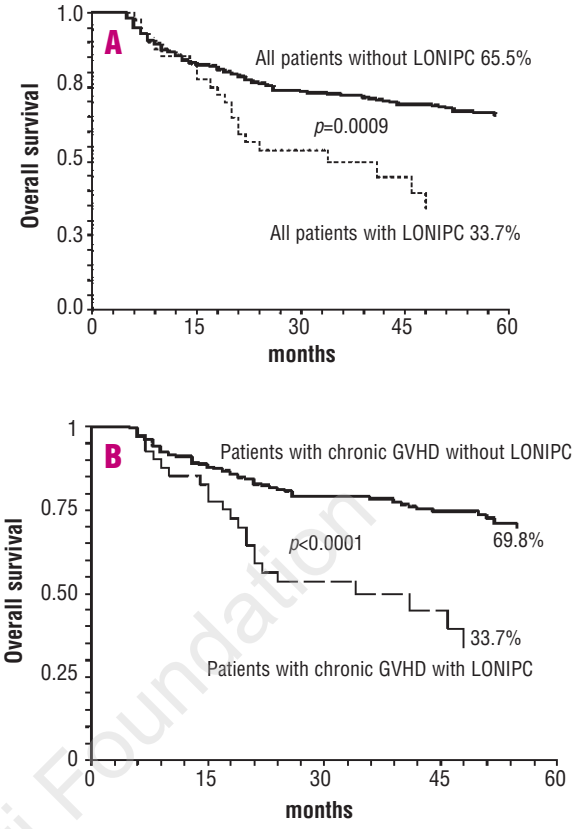

Figure 1. Comparison of 5-year overall survival between patients with and without LONIPC among (A) all transplanted patients and among (B) patients with chronic GVHD.

variate analysis at the time of chronic GVHD. The first-line therapy was cyclosporine A plus prednisone (1-2 mg/kg/day) in 26 patients (64%), cyclosporine A alone in two patients (5%), prednisone alone in five patients (12%), prednisone plus mycophenolate mofetil in three patients (7%), cyclosporine A plus prednisone plus mycophenolate mofetil in five patients (12%). Fifteen patients (36%) were responsive to first line therapy, ten (24%) having a complete response and five (12%) having a partial response. Two other patients had a short-lasting partial response and then progressed: therefore, they were included in the group of the 26 (64%) unresponsive patients. Fourteen unresponsive patients (34%) received salvage therapy based on the association of a third drug (methotrexate or thalidomide, mycophenolate mofetil, azathioprine, rituximab) to cyclosporine A plus prednisone. Twelve unresponsive patients (30%) received no salvage therapy because they died before any treatment was initiated. Six out of 26 (23%) non-responsive patients achieved a partial response with salvage therapy. Overall, 21 patients (51%) achieved a response; this was complete in 10 patients (24%) and partial in 11 patients (27%). At a median follow-up of 14 months (range, 1-113) after the diagnosis of LONIPC 23 patients (56%) had died. Causes of death were respiratory failure in 13 patients (56%), infections in five patients (22%), and relapse in the other five patients (22%). The 5-year overall survival was significantly worse in patients with LONIPC than in those without (Figure 1A). Moreover, a significant reduction of survival was observed in patients with LONIPC in comparison with that in all patients affected by chronic GVHD (Figure 1B). Patients who subsequently developed fatal respiratory insufficiency were more likely to be young (median age 29 vs 40 years; p=0.03), transplanted from an unrelated donor (77% vs 49% unrelated donor; p=0.04)

and unresponsive to first-line treatment with cyclosporine A and/or prednisone (100% vs 39%; p=0.02) than patients alive or dead because of other causes.

In our study , we found a true incidence of LONIPC of 10%, which is largely consistent with the incidences reported in the literature, which vary between 10%[2] and 23%.[6] We confirmed our previous observation[7] that transplants from unrelated donors were associated with a higher risk of developing LONIPC and in the present series also with a higher risk of death because of respiratory insufficiency. Previous studies have consistently found an association between LONIPC and chronic GVHD,[2,7-14] but a relationship with acute GVHD was present in some studies[10,15] and absent in others.[7,11] Our analysis showed that chronic GVHD in its extensive form was a powerful risk factor for the further development of LONIPC, whereas neither acute GVHD alone nor pre-existing acute GVHD altered the risk for the development of LONIPC. It may be hypothesized that, despite the well established clinical association between acute and chronic GVHD , the pathogenesis of chronic GVHD, which has distinctive clinical and pathological manifestations that mimic autoimmune diseases, is probably different. Nearly half of the patients responded to immunosuppressive treatment, which consisted of conventional drugs, namely cyclosporine A and/or prednisone in about 80% of them. We found that responsiveness to first-line treatment was crucial for the outcome, since it was associated with a significant reduction in the risk of death from respiratory failure. We could not evaluate the efficacy of salvage treatment with rituximab, mycophenolate mofetil or thalidomide, suggested to be effective in case reports and small series of patients affected by extensive chronic GVHD,[16,17] since the drugs associated as third choice were heterogeneous and the number of treated patients was small. In our series patients with LONIPC had a significantly worse 5-year survival that that of patients without LONIPC. In most studies there was no excess of mortality in the population affected by LONIPC[10,11,13] in comparison with unaffected subjects. The similar survival curves between patients with and without LONIPC were explained by Sakaida *et al.*[13] by the observation that a higher number of deaths due to respiratory failure were counterbalanced by fewer deaths due to relapse of the primary malignant disease, suggesting a benefit of the graft-versus-leukemia effect. In contrast, in our study the relapse rate of the primary hematologic disease was similar in patients with and without LONIPC and mortality was mostly due to respiratory failure or infections.

Our study has several limitations . Firstly, the diagnosis of LONIPC was based on the clinical, radiological and functional criteria identified by Palmas *et al.* in 1998[2] and was supported by consistent histological data in 25% of all cases of LONIPC and in 39% of cases of BOOP and IP. This limitation was present in the majority of the previous studies, in which a histological diagnosis was obtained only in a proportion of the cases varying between 27% (13) and 61%.[2] There are several possible reasons for the lack of a consistent histological diagnosis, such as the unsatisfactory diagnostic yield and the still high rate of complications of biopsies.[17,18] Secondly, we failed to identified differences in risk factors, response to therapy and outcome among BO , BOOP and IP, in part probably because of the small number of patients examined.

In conclusion, our study has demonstrated a significant increase of the risk of LONIPC in patients with extensive chronic GVHD and after transplants from unrelated donors. The development of LONIPC significantly reduced survival: patients who did not respond to enhanced immunosuppressive treatment were at the highest risk of death because of respiratory insufficiency. Further studies should focus on the clinical and functional monitoring of patients with one or more risk factors in an attempt to recognize and treat this respiratory complication earlier.

FP: responsible for the main design of the study and writing the paper; CS: responsible of the statistical analysis and collaborated in writing the paper; FB: collaborated in the design of the study, in the statistical analysis and and in writing the paper; AS: involved in the clinical follow-up of the patients, in the collection and in the interpretation of functional and pathological data; GB: involved in the interpretation and revision of the data and writing in the final version of the manuscript; MC: involved in the collection and in the interpretation of the data; AG: involved in the clinical follow-up of the patients, in the collection and interpretation of functional and pathological data; FZ: involved in the statistical analysis and in writing the manuscript; CF: was involved in the clinical follow-up of the patients, in the collection and interpretation of functional and pathological data; MB: chief of one of the Instututions in which the study was carried and involved in the revision and final version of the paper; RF: chief of one of the Instututions in which the study was carried and involved in the revision and final version of the paper.

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