Pediatr Transplantation 2009: 13: 719–724



Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2008.01055.x

# Cardiac and pulmonary late effects do not negatively influence performance status and non-relapse mortality of children surviving five yr after autologous hematopoietic cell transplantation: Report from the EBMT Paediatric Diseases and Late Effects Working Parties

Uderzo C, Pillon M, Tridello G, Dini G, Urban C, Corti P, Zintl F, Fagioli F, Messina C, Verdeguer A, Faraci M, Fedeli S, Tana F, Tichelli A, Passweg J, Rovelli A. Cardiac and pulmonary late effects do not negatively influence performance status and non-relapse mortality of children surviving five yr after autologous hematopoietic cell transplantation: Report from the EBMT Paediatric Diseases and Late Effects Working Parties.
Pediatr Transplantation 2009: 13: 719–724. © 2008 John Wiley & Sons A/S.

Abstract: The current prospective study dealt with clinical outcome associated with pulmonary and cardiac late effects of AuHCT in children with malignancies. We prospectively evaluated 58 children, utilizing pulmonary function tests and cardiac shortening fraction, performed in pre-AuHCT phase and then annually. The overall five-yr survival was 68%. The five-yr cumulative incidence of lung and cardiac function impairment in survivors was 21% in both cases. None of the patients presented with restrictive or obstructive pulmonary pathology at the last follow-up and performance status for all survivors, ranged from 90% to 100%. The cumulative incidence of non-relapse mortality was 12.6% (range 6.3–25.3%), whereas relapse mortality was 19.7% (range 11.6–33.5). In conclusion, our study shows no significant deterioration in post-AuHCT pulmonary and cardiac function and in particular, no negative impact of lung and heart late effects on performance status and non-relapse mortality.

**Cornelio Uderzo[1], Marta Pillon[2], Gloria Tridello[2], Giorgio Dini[3], Christian Urban[4], Paola Corti[1], Felix Zintl[5], Franca Fagioli[6], Chiara Messina[2], Amparo Verdeguer[7], Maura Faraci[3], Sara Fedeli[1], Francesco Tana[8], André Tichelli[9], Jakob Passweg[10] and Attilio Rovelli[1]**

[1]Centro Trapianti di Midollo Osseo, Clinica Pediatrica, Dipartimento Cardio-Toracico, Ospedale San Gerardo di Monza, Università di Milano Bicocca, Italy, [2]Clinica di Oncoematologia Pediatrica, Dipartimento di Pediatria, Università di Padova, Italy, [3]Dipartimento di Ematologia ed Oncologia, IRCCS "G. Gaslini", Genova, Italy, [4]Division of Pediatric Hematology/Oncology, University Children's Hospital, Graz, Austria, [5]Department of Pediatrics, Jena University, Germany, [6]Dipartimento di Pediatria, Ospedale Regina Margherita, Università di Torino, Italy, [7]Oncologia Pediatrica, Hospital Infantil La Fe Valencia, Spain, [8]Reparto di Pneumologia, Dipartimento Cardio-Toracico, Ospedale San Gerardo di Monza, Università di Milano Bicocca, Italy, [9]Department of Haematology, University Hospital, Basel, Switzerland, [10]Department of Medecine Interne, Hopitaux Universitaires de Geneva, Geneva, Switzerland

Key words: pulmonary – cardiac late effects – autologous hematopoietic cell transplantation – childhood – performance status

Cornelio Uderzo, Pediatric Department, HSCT Unit, S. Gerardo Hospital, University of Milano Bicocca, Via Pergolesi 33, 20052 Monza (Milan), Italy
Tel.: +39 039 2332442
Fax: +39 039 2301646
E-mail: cornelio.uderzo@pediatriamonza.it

Accepted for publication 11 August 2008

Abbreviations: AHCT, allogeneic hematopoietic cell transplantation; AuHCT, autologous hematopoietic cell transplantation; EMBT, European Bone Marrow Transplantation; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndromes; MOF, multiorgan failures; NHL, non-Hodgkin's lymphoma; OS, overall survival; PFT, pulmonary function tests; SF, shortening factor; TBI, total body irradiation; VC, vital capacity.

Despite the fact that AuHCT has a different role compared with AHCT, over the last 20 yr, it has contributed to the cure of a number of patients affected with solid tumors, relapsed lymphomas or acute leukemia. To the best of our knowledge, there are no reports addressing late or very late lung and heart functioning complications in children who received AuHCT for hematological malignancies. However, children who survived after AHCT have been reported to complain of late congestive heart failure but not of life-threatening respiratory failure (1).

Having recently described the impact of some risk factors on pulmonary and cardiac functioning in children who underwent AHCTs (2), in this report, we present the results of a five-yr evaluation of pulmonary and cardiac function in children who underwent AuHCT in the same period as the previous report. This prospective study was conducted on behalf of EBMT Paediatric Diseases and Late Effects Working Parties with the aim of dealing with specific aspects of lung and heart functional status in survivors of AuHCT performed in childhood. Particular emphasis was devoted to the impact of possible lung and heart function alteration on non-relapse mortality and on performance status.

## Patients and methods

This collaborative study evaluated 58 consecutive pediatric patients who underwent AuHCT and survived at least five yr after transplantation performed for malignant diseases in seven EBMT centers. Our report was restricted to individuals who met the following eligibility criteria:

(a) primary diagnosis of a malignant disease, including MDS because some European HCT centers performed autologous transplantation in patients affected with MDS at that time;
(b) all AuHCTs were consecutively performed between January 1994 and January 1998 in children from birth to 18 yr old. Patients recruited were requested to perform standardized PFTs including VC%, FVC%, and FEV1% (3, 4).

Patients were considered to have normal PTFs when VC and FEV1 values were $>80\%$ or when VC was $>80\%$, FEV1 $> 70\%$ and FEV1%/FVC% was $>90\%$. We defined "restrictive syndrome" as being when VC% was $<80$ and FEV1%/FVC% $>90$ and "obstructive syndrome" when VC% was $>80$, FEV1% $< 80$, FEV1%/FVC% $< 90$ or VC% $> 80$, FEV1% $> 80$ and FEV1%/FVC% $< 90$. If VC% was $<80$ and FEV1%/FVC% $< 90$, it was not possible, in absence of total lung capacity, to separate a mixed pattern from an obstructive pattern associated with hyperinflation.

Cardiac evaluation was performed using a two-dimensional M-Mode echocardiogram to obtain information regarding dimensions, volumes, ventricular systolic function and cardiac mass (5). Even in the presence of SF $> 30\%$, patients' cardiac functioning was normal. Given its well-known cardiac toxicity, the total dose of anthracyclines was requested in the data collection form. PFTs and cardiac function surveillance were obtained as described in the methods section of our previous report (2), initially pre-AuHCT and then annually at least up to the five-yr post-AuHCT.

The study investigators registered patient demographics and clinical characteristics, including severe lung and heart abnormalities and every cause of death which occurred after AuHCT. As almost all patients were adolescents or young adults at the end of the study, they were evaluated by means of either the Lansky ($<16$ yr old) or Karnofsky performance score ($>16$ yr) (6).

The above scores were assigned in increments of 10%. Scores of 90% and 100% were compatible with normal activity; a score $\leq 80\%$ reflected progressive efforts to continue with normal activity. Patients less than six yr old at the beginning of the study were not allowed to perform PFTs because of their age. The Human Subjects committees of the participating centers approved the study and an informed consent was obtained for each child enrolled, according to the declaration of Helsinky.

### Statistical analysis

Data were revised up to January 2007 and then analyzed. The probability of PFTs or SF abnormalities and annual time units hazard rate were calculated using cumulative incidence-life table method based on discrete data collected yearly (7). ANOVA analysis was used to compare test values (VC, FEV1 and SF) at each evaluation during the follow-up (8). The probability of OS from the date of AuHCT to the date of death or the date of last follow-up was calculated using the Kaplan–Meier estimator. The cumulative incidence of non-relapse mortality was calculated using the cumulative incidence-function method (7). The statistical analysis was performed using the SAS statistical program (Version 8.2; SAS Institute, Cary, NC, USA) and NCSS (Number Cruncher Statistical Systems, Kaysville, UT, USA).

## Results

Patients' characteristics, such as age, gender, diagnosis, status of hematological remission at AuHCT, pretransplant anthracycline therapy or type of conditioning regimen with or without TBI, are summarized in Table 1. The source of stem cells was bone marrow and peripheral blood in all patients. Forty-six of 58 patients received anthracyclines with a median dose of 233 mg/m$^2$ (range 30–550), while 15/46 received more than a 300 mg/m$^2$ anthracyclines cumulative dose.

Twenty-six patients underwent fractionated TBI combined with high dose chemotherapy, which included cyclophosphamide with or without VP-16. Thirty-two children underwent high dose chemotherapy only, which primarily consisted of cyclophosphamide, busulphan and, for acute or chronic myeloid leukemia, melphalan

Table 1. Patient characteristics

| | | No. of patients |
|---|---|---|
| Gender | Male/female | 28/30 |
| Median age in yr (range) at AuHCT | | 12.1 (1–17.9) |
| Diseases | Diagnosis | 58 |
| | Acute lymphoblastic leukemia | 17 |
| | Acute myeloid leukaemia | 19 |
| | Chronic myelogeneous leukaemia | 1 |
| | Non-Hodgkin lymphoma | 2 |
| | Hodgkin lymphoma | 4 |
| | Neuroblastoma | 4 |
| | Myelodysplastic syndrome | 11 |
| Anthracyclines | Yes/no | 46/12 |
| TBI | Yes/no | 26/32 |
| Status at AuHCT for malignant diseases | First or second CR/other CR | 47/11 |

AuHCT, autologous hematopoietic stem cell transplantation; CR, complete remission; TBI, total body irradiation.

combined regimen. The OS at five yr was 68% (95% CI 55–80).

At the last follow-up, 40/58 patients were alive and well with a median Lansky or Karnofsky score of 100% (range 80–100). Eighteen patients died at a median time of 1.1 yr post-AuHCT (range 86 days–4 yr). Causes of death was disease relapses (11), MOF (two), infectious diseases (four) and veno-occlusive disease (one). Six of these 18 patients, including one whose death resulted from MOF, had SF or PFT abnormalities only at baseline assessment. The cumulative incidence of non-relapse mortality was 12.6% (95% CI 6.3–25.3%), whereas relapse mortality was 19.7% (95% CI 11.6–33.5%).

### Evaluation of PFTs

Information regarding VC or FEV1 tests was collected at the time of AuHCT in 47/58 patients, but complete data, sufficient to define the normality of PFTs were available for just 36/47. At baseline assessment, 10/36 patients presented with PFT values slightly below the optimal range. The five-yr cumulative incidence of respiratory function abnormalities of the 26 patients with normal basal values was 21% (Fig. 1a). During follow-up, the number of patients decreased from 26 to 17 because of AuHCT-related death (three cases) or lack of information on PFTs (six cases). Hazard rate was remarkable at the first yr post-transplant (0.08); none of the patients fully evaluated at the five yr presented with pulmonary restrictive or obstructive abnormalities. Beyond that, all patients showed a median Lansky or Karnofsky performance score of 100% (90–100) with normal quality of life.

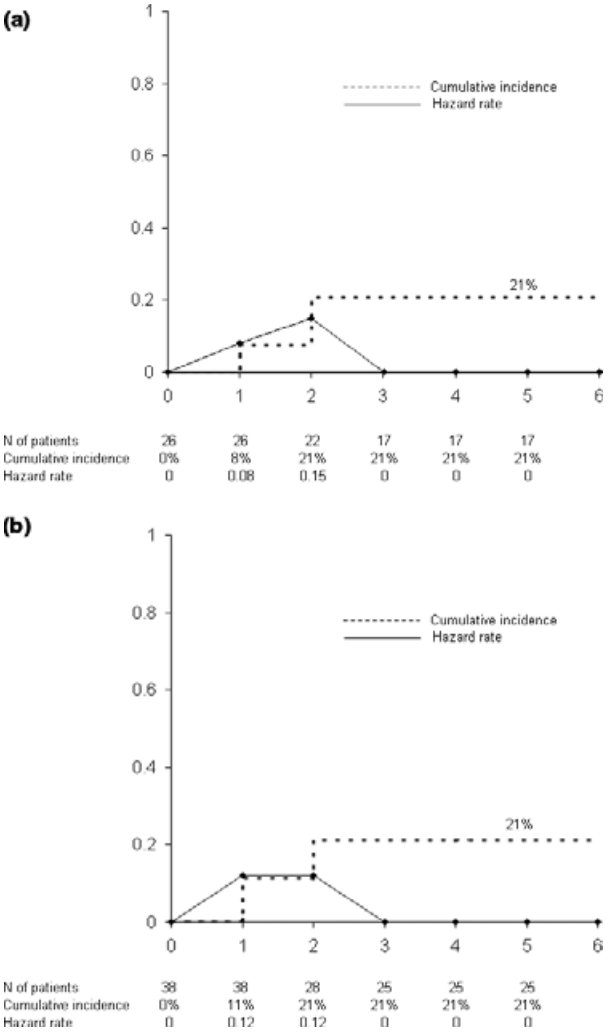


*Fig. 1.* (a) The annual cumulative incidence and hazard rate of pulmonary function tests abnormalities were calculated on 26 patients with normal values at baseline. Every pattern different from VC >80% or FEV1% >70% or FEV1%/FVC% > 90% was considered an event. (b) The annual cumulative incidence and hazard rate of cardiac abnormalities were calculated on 38 patients with normal values of SF at baseline. A SF value <30% was considered an event.

None of the patients who died were affected by late pulmonary complications or lung infections. The yearly mean values and standard errors of VC and FEV1, analyzed separately, are presented in Fig. 2a and b, respectively. The decrease of mean values was not statistically significant in both cardiac function test and PFTs evaluation.

Information regarding SF test was available for 41 out of 58 patients. At the time of AuHCT, three of 41 patients had an abnormal SF test; one died of MOF during infectious disease, one improved his SF and the last one showed mild SF abnormalities at the last follow-up. The remaining 38/41 patients had normal basal tests

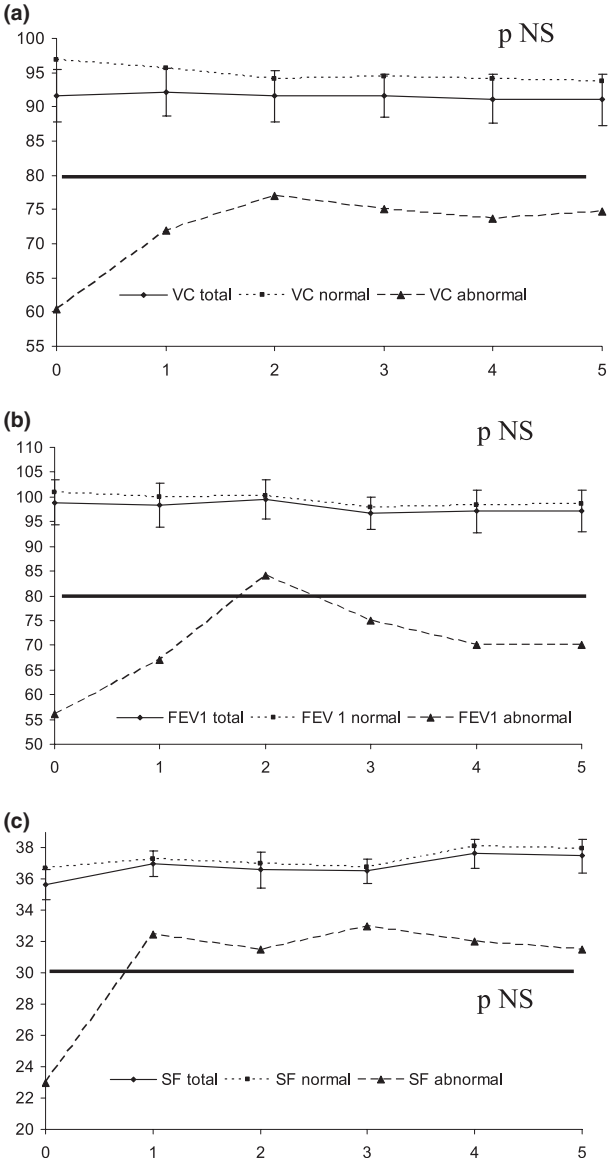


*Fig. 2.* (a) Twenty-one patients (18 with normal and three with abnormal VC tests at AuHCT) are described with available data on VC tests. (b) Twenty-one patients (20 with normal and one with abnormal FEV1 tests at AuHCT) are described with available data on FEV1 tests. (c) Twenty-seven patients (25 with normal and two with abnormal SF tests at AuHCT) are described with available data on SF tests.

during the five yr of observation and presented a cumulative incidence of SF abnormalities of 21% (Fig. 1b). At the five yr, 25/38 patients with normal basal SF were alive, 5/38 patients died, but none because of late cardiac dysfunction and SF information was missing for 8/38 patients during the follow-up. Overall, just 2/25 patients surviving to the five yr, presented with asymptomatic cardiac abnormalities. The surviving patients have a median performance score of 100% (range 90–100).

ANOVA analysis was applied to the 25 patients with normal SF test and to the two patients with SF $< 30\%$ at baseline evaluation (Fig. 2c). The decrease of mean values was not statistically significant. Given the limited number of events throughout the study, the risk factor analysis was not performed.

## Discussion

Our primary goal was to prospectively assess and delineate late pulmonary and cardiac function deterioration in patients who underwent AuHCT during childhood and who were all studied similarly, up to adolescence or a young adult age. In the current study, the cumulative incidence of asymptomatic lung and heart late sequelae was 21%, with hazard rate decreasing to zero at the five yr for both organs. The median level of performance Lansky or Karnofsky status at five yr was 100%, indicating no negative, long-term impact of AuHCT transplant-related toxicity. Allogeneic patients treated at the same EBMT centers during the same period, showed a higher cumulative incidence of these late effects. In particular and not unexpectedly, pulmonary function was more greatly affected (2), as a result of the allogeneic effect of GVHD.

Despite our findings, we are aware that more sophisticated functional tests, such as exercise tests (9, 10), should be done, to better monitor cardiac or pulmonary performance in adolescent survivors of AuHCT. The fact that no moderate or severe cardiac or pulmonary pathologies were noted during follow-up in our series, may represent a relatively optimistic message for those clinicians who have to make a decision before AuHCT, even in patients receiving significant pre-AuHCT chemotherapy. In our study, only a few patients presented abnormal basal pre-AuHCT PFTs or SF tests and none showed functional deterioration or clinical symptoms at the end of the long follow-up period. Besides that, we agree with other authors who stated that an impaired left ventricular ejection fraction at the time of transplant doesn't constitute a reliable risk factor in the early post-transplant period (11). In line with the European and American Marrow Transplantation Societies guidelines (12), we suggest continuous follow-up only for those few adolescents or young adults who show a pattern of minimal pulmonary and cardiac function deterioration, five yr post-AuHCT. Even though cardiovascular late effects seem to be more frequent and risky in AHCT series compared with AuHCT series, as seen in a recent large survivor study, which only included transplanted

adult patients (13), long-term cardiovascular outcome should, however, be studied in younger patients, such as ours, to draw any definitive conclusions.

A recent Childhood Cancer Survivor Study which provided results concerning late mortality and second cancers in pediatric patients with NHL, showed that female gender, cardiac radiotherapy exposure and treatment with anthracyclines, were associated with an increased relative risk of mortality from causes other than NHL (14). However, in a multivariate model including all these factors, the same study claimed that only female gender and cardiac radiotherapy exposure were predictors of late mortality. The analysis of risk factors was not performed because of the limited number of events, which could be a limitation of this study, even though the report is unique as far as type of transplant and pediatric case series long-term pulmonary and cardiac function outcome are concerned.

On the other hand, an interesting finding in the era of continuous improvement of outcome among transplanted patients was the lack of any negative impact of late cardiac and pulmonary effects on non-relapse mortality. This is in contrast with a large study involving adult AuHCT patients (15), which demonstrated that 2% of the long-term survivors died from cardiac and pulmonary toxicity. Moreover, a 4.4-fold death risk for cardiac causes in females and 6.7-fold death risk for pulmonary causes in males, was reported in that study, throughout the years. Another recent study with case-matched controls (16), involving adult survivors after 10 yr showed limited statistical power in detecting a correlation between late cardiac or pulmonary complications and non-relapse mortality, mainly because of the small number of AuHCT patients. However, there are a few studies which indicate that post-transplant abnormal PFTs have predictive values for AHCT outcome in adult patients, mostly because of chronic GVHD and severe airflow obstruction (17, 18).

In conclusion, our study underlines a comprehensive normal pattern of late pulmonary and cardiac function in pediatric patients who received an AuHCT for malignant diseases. Autologous procedures and associated cardiopulmonary late effects did not affect non-relapse mortality in the long-term, diversely from what has been observed in adult recipients. The good performance status at the five-yr post-transplant, suggests that AuHCT long-term adolescent survivors, could have optimal physical and social activity. Finally, for these patients, a lifelong commitment with the transplant center is necessary, because we do not know whether late cardiopulmonary complications in children who are expected to become very long-term survivors, can occur decades after HCT.

## Acknowledgments

The principal investigator is indebted to Prof. Hans-Jochem Kolb (Munich) for his own contribution in the early stage of the project and Joanna Upton for reviewing the manuscript.

## Contributions to data collection

Monza: Marco Nuara, MD, Barbara Nicolini, MD; Torino: Eugenia Maria Saroglia, MD; Padova: Stefania Varotto; Genova: Edoardo Lanino, MD and Luca Manfredini, MD; Jena: Lothar Vogt, MD and Isabella Schiller.

## Conflict of interest

Each author warrants that he or she has no commercial associations that might pose a conflict of interest in connection with the submitted article.

## References

1. Ness KK, Bhatia S, Baker KS, et al. Performance limitations and participation restrictions among childhood cancer survivors treated with hematopoietic stem cell transplantation. Arch Pediatr Adolesc Med 2005: 159: 706–713.
2. Uderzo C, Pillon M, Tridello G, et al. Impact of anthracycline dose, preparative regimen and chronic graft-versus-host-disease on pulmonary and cardiac function in children 5 years after allogeneic hematopoietic stem cell transplantation: A prospective evaluation on behalf of the EBMT Pediatric Diseases and Late Effects Working Parties. Bone Marrow Transplant 2007: 39: 667–675.
3. Hankinson JL, Bang KM. Acceptability and reproducibility criteria of the American Thoracic Society as observed in a sample of a general population. Am Rev Resp Dis 1991: 143: 516–525.
4. Gardner RM, Hankinson JL, Clausen L, et al. Standardisation of spirometry: 1987 Update. Official statement of the American Thoracic Society. Am Rev Resp Dis 1987: 136: 1285–1298.
5. Rovelli A, Pezzini C, Silvestri D, et al. Cardiac and respiratory function after bone marrow transplantation in children with leukemia. Bone Marrow Transplant 1995: 16: 571–576.
6. Blume KG, Amylon MD. The evaluation and counseling of candidates for hematopoietic cell transplantation. In: Blume KG, Forman SJ, Appelbaum FR, eds. Thomas' Hematopoietic Cell Transplantation, 3rd edn. Blackwell Science, Malden, MA: 2004: pp. 449–461.
7. Marubini E, Valsecchi MG. Analysing Survival Data from Clinical Trials and Observational Studies. Chichester, NY: Wiley & Sons, 1995.
8. Armitage P. Statistica Medica: Metodi Statistici per la Ricerca in Medicina. Italy: Edizioni Feltrinelli, 1985.
9. De Wolf D, Suys B, Maurus R, et al. Dobutamine stress echocardiography in the evaluation of late anthracycline cardiotoxicity in childhood cancer survivors. Pediatr Res 1996: 39: 504–512.
10. Hogarty AN, Leahey A, Zhao H, et al. Longitudinal evaluation of cardiopulmonary performance during exercise after bone marrow transplantation in children. J Pediatr 2000: 136: 311–317.

11. Tang WHW, Thomas S, Kalaycio M, et al. Clinical outcomes of patients with impaired left ventricular ejection fraction undergoing autologous bone marrow transplantation: Can we safely transplant with impaired ejection fraction? Bone Marrow Transplant 2004: 34: 603–607.
12. Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practice for long-term survivors after hematopoietic cell transplantation: Joint recommendations of the European Group for Blood and Marrow Transplantation Centers for International Blood and Marrow research and the American Society for Blood and Marrow Transplantation (EBMT/CIBMTR/ASBMT). Bone Marrow Transplant 2006: 37: 249–261.
13. Baker KS, Ness KK, Steinberger J, et al. Diabetes, hypertension and cardiovascular events in survivors of hematopoietic cell transplantation: A report from the bone marrow transplantation survivor study. Blood 2007: 109: 1765–1772.
14. Bluhm EC, Ronckers C, Hayashi R, et al. Cause-specific mortality and second cancer incidence after non-Hodgkin lymphoma: A report from the Childhood Cancer Survivor Study. Blood 2008: 111: 4014–4021.
15. Bhatia S, Robison LL, Francisco L, Carter A, et al. Late mortality in survivors of autologous hematopoietic-cell transplantation: Report from the bone marrow transplant survivor study. Blood 2005: 105: 4215–4223.
16. Syrjala KL, Langer SL, Abrams JR, Storer BE, Martin PJ. Late effects of hematopoietic cell transplantation among 10-year adult survivors compared with case-matched controls. J Clin Oncol 2005: 23: 6596–6606.
17. Crawford SW, Pepe M, Lin D, Benedetti F, Deeg HJ. Abnormalities of pulmonary function tests after bone marrow transplantation predict non relapse mortality. Am J Respir Crit Care Med 1995: 152: 690–695.
18. Chien JW, Martin PJ, Gooley TA, et al. Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. Am J Respir Crit Care Med 2003: 168: 208–214.