

Secondary malignancies and quality of life after stem cell transplantation

JJ Ortega, T Olivé, CD de Heredia and A Llorca

Department of Pediatric Hematology/Oncology, Hospital Universitari, Vall d'Hebron, Barcelona, Spain

Summary:

Malignant diseases (MD) occurring after stem cell transplantation (SCT) are of particular concern as increasing number of patients survive and remain free of their original disease. The cumulative incidence at 15 years is 10–12%. The B-cell proliferative disorders (BCLP) are the most common MD in the first year after SCT; the incidence probability is 1% in allogeneic transplants but is much higher (until 14%) after HLA-identical, T-cell-depleted SCT in which Campath 1G or ATG are given. BCLP develop because of reactivation of the EBV and a depressed cellular immunity. Prediction of risk of BCLP can be made by frequent monitoring of EBV load in patients with risk factors. The most effective therapies are the early administration of anti-CD20 monoclonal antibody and adoptive immunotherapy with *in vitro* generated EBV-specific cytotoxic T cells. Myelodysplasia and acute myeloid leukemia with very poor prognosis have been described in 4–18% of patients with non-Hodgkin lymphoma and Hodgkin disease, 12–24 months after autologous SCT. The risk of development of solid tumors increases over time and the cumulative incidence among children who underwent an SCT at less than 10 years of age is 6–11% at 15 years. There are few studies evaluating quality of life (QOL) in children and adolescents who had received an SCT. The findings of these studies can be summarized as follows: (a) The majority of long survivors enjoy good QOL and return successfully to school or work. (b) A minority (10–15%) complain of physical problems or present moderate cognitive or psychological dysfunctions. (c) The importance of family, other social support and psychological adjustments is generally recognized. More extensive, longitudinal and comparative studies with other alternative therapies are required.

Bone Marrow Transplantation (2005) 35, S83–S87.

doi:10.1038/sj.bmt.1704854

Keywords: secondary malignancies; BMT (SCT); children; lymphoproliferative disorders; solid tumors; quality of life

Secondary malignancies

Among the late effects described after SCT, malignant diseases are of particular concern as increasing numbers of patients survive the early phase after transplantation and remain free of their original disease.

The magnitude of risk of secondary malignancies after SCT, measured by the ratio of observed incidence to the expected incidence in the general population of same age and sex, shows a RR of 4–11-fold in several studies and the cumulative incidence at 15 years is 10–12%.^{1–4}

The main factors for developing secondary malignancies are intensive cytotoxic conditioning therapy and previous chemotherapy and radiotherapy, immunosuppression in allogeneic transplants, infection with viruses such as EBV, HBV and HCV and genetic factors in certain diseases (Fanconi anemia).⁴

Secondary malignancies are commonly classified in three groups: (1) myelodysplasia (MDS) and acute myeloid leukemia (AML); (2) B-cell post-transplant lymphoproliferative disorders (BCLD) and (3) solid tumors (ST).

MDS, AML and BCLD develop relatively early in the post transplant period but ST have a longer latency time.

Myelodysplasia and AML

The *cumulative probability* of both disorders after autologous SCT for non-Hodgkin lymphoma (NHL) or Hodgkin disease (HD) ranges from 4 to 18%. The median time to development is 12–24 months after SCT.^{1,4–6}

The *Risk factors* include:⁴

- pre-transplantation therapy with alkylating agents, topoisomerase II inhibitors and radiation therapy;
- use of peripheral blood as source of stem cells;
- use of TBI in conditioning.¹

The prognosis is very poor with a median survival of 6 months.⁴ Complete remission is attained in only 35–40% and patients receiving an allogeneic SCT have a very high rate of nonrelapse mortality.⁷ Nevertheless, if an appropriate donor is available, patients without a high peripheral blast count and with unfavorable cytogenetics should be considered for a prompt transplantation. Use of reduced-intensity conditioning may result in improved outcomes by reducing the nonrelapse mortality.

BCLD

BCLD are the most common secondary malignancies in the first year after allogeneic T-cell-depleted SCT. Most cases are related to compromised immune function and EBV infection. The large majority of lymphoproliferative disorders are of B-cell origin and usually develop within the first 6 months after SCT.⁴

Clinically and morphologically BCLD is a heterogeneous group of diseases.

The incidence probability is about 1% in allogeneic transplants,^{1,4,8,9} but is much higher (until 14%) after non-HLA-identical, T-cell-depleted bone marrow transplants in which Campath IG and anti-LFA 1 were given.¹⁰

Risk factors associated with higher probability of development of BCLD are:^{4,8}

(a) *in vitro* T-cell depletion; (b) unrelated or HLA-mismatched related donor, (c) moderate or extensive chronic GVHD; (d) use of ATG or anti-CD3; (e) use of TBI in the preparative regimen; (f) primary immunodeficiency.

Pathogenesis: BCLD develop because of a combination of depressed EBV-specific cellular immunity and reactivation of the transforming capacities of EBV. The EBV infects a large proportion of individuals and persists as a latent infection in B-cell lymphocytes. Reactivation may occur when cytotoxic T-lymphocyte precursors frequencies are very low.

Prediction of risk of BCLD can be done by frequent monitoring of EBV load in peripheral blood by Q-PCR in patients with risk factors.¹¹ Rapid increases in EBV-DNA load predict BCLD and allow that therapy be started before the development of open disease.

Treatment. A combination of alpha-interferon and intravenous immunoglobulin was used with some positive results,¹² but the most effective therapies are the administration of anti-B monoclonal antibodies¹³ and the use of *in vitro* generated EBV-specific cytotoxic T cells.^{14–16}

Several studies have reported the efficacy of anti-CD20 monoclonal antibody (rituximab). In one study, 12 children with post transplant BCPD received rituximab eight attaining a complete remission with normalization of EBV load.¹⁵ The drug is well tolerated and more efficacious in patients without mass lesions. The recommendation is to initiate treatment at an early stage. Adoptive immunotherapy with cytotoxic T-cell therapy has been shown to be efficacious in controlling BCLD with a decrease in the EBV DNA concentrations and a remission of clinical signs and symptoms.^{4,14,16,17} This treatment appears to be safer and more effective used as prophylaxis or as treatment in early stage of development.

ST

Patients who have received an SCT are at higher risk (2.1–2.7) for development of ST. The risk increases over time and is higher among children who underwent an SCT at less than 10 years of age. *Cumulative incidences* at 15 years is 6–11%.^{1–4,9,18,19}

In a cohort of 3182 children with acute leukemia, who received an allogeneic SCT before 17 years of age at 325 centres between 1964 and 1992, 25 ST were observed compared with one case expected. The donor types were an HLA-identical sibling in 79%, a mismatched related in 15% and a matched unrelated in 3%. The cumulative incidence of solid tumours at 15 years was 11% (CI 2.3–19.8%). The median time from SCT to tumor was 6 years (0.3–14 years) and was highest at ages younger than 5 years at transplantation. Many of these patients had received cranial irradiation before SCT. Multivariate analysis showed that high-dose TBI (more than 10 Gy in one dose or more than 13 Gy in fractionated dose) and younger age at SCT (less than 10 years) were risk factors, whereas chronic GVHD was associated with lower risk.⁹ Significantly elevated risks were observed for cancers of the tongue (O/E = 2765), salivary glands (O/E = 519), thyroid (O/E = 125) melanoma (O/E = 65) and brain and CNS (O/R = 46).⁹

In other study, the incidence and risk factors for the development of malignancies after SCT in 700 patients with severe aplastic anemia were analyzed; in 79 cases, the etiology was genetic, Fanconi anemia. A total of 18 patients developed ST (squamous cell carcinoma in 17) localized in head and neck (11), skin (6) and vulva (1). Five patients with Fanconi anemia developed head and neck carcinomas from 6 to 11 years after SCT. Risk factors for all the series included diagnosis of Fanconi anemia and irradiation.²⁰

Little is known about the pathogenesis of ST after SCT, but an interaction of cytotoxic therapy, genetic predisposition, viral infection, GVHD and use of immunosuppressive therapy seem to have a role.⁴

The ST secondary to SCT must be treated as *de novo* tumors. Early detection and intensive treatment may favor a good outcome.²¹

Conclusion. The incidence of post transplant malignancies is relatively low although estimates of the overall risk require a long follow-up. It is imperative to follow this population of SLT recipients for 15–20 years at least.

Quality of life studies

The definition of health-related quality of life (QOL) refers to the extent to which the usual or expected physical, emotional and social well-being of a person are affected by a medical condition or its treatment.²²

Cross-sectional and longitudinal surveys have been performed mainly in adults from pre-transplant through 10 years post transplant. The findings of these QOL studies have showed that^{22–24}

- (1) Physical function returns to pre-transplant level for 75% of survivors by 1 year.
- (2) By 3 years, 80–90% of survivors are back to full-time work.
- (3) The majority of patients have good psychological health.
- (4) A minority of patients have major residual problems with a variety of QOL functions.

- (5) A large majority of adult survivors of HCT function well in the domains of physical, psychological, social, existential and overall subjective QOL.

There are few studies evaluating QOL in children and adolescents who had received an SCT and, with a few exceptions, are limited to cross-sectional surveys. These studies deal with intelligence tests, school performance, social functioning with family and friends, self-esteem, body image and physical performance.^{25–29}

A few sequential studies have assessed the health-related QOL pre-HCT through 6 months post transplant. Phipps *et al*, in Memphis, studied somatic distress, compliance, mood disorders and quality of interaction in 153 children undergoing BMT between 1995 and 1998. The findings were that children entered the hospital for transplant with heightened levels of distress, which increased following conditioning and until 1 week following transplant. The distress decreased to admission levels by week +4 and had a further decline at 4–6 months. Determinant factors with negative influence on patient response were: (a) *type of transplant*, allogeneic transplants compared with autologous and unrelated *vs* identical sibling donor; (b) *age*, younger patients experiencing lower levels of distress and better QOL than older children and adolescents; (c) *socioeconomic status* (SES) with patients from lower SES demonstrating greater distress and disturbance in health-related HR-QOL. IQ scores remained stable during the first year post transplant.³⁰

In a similar study performed by Barrera *et al*, from Toronto, 26 children who underwent a BMT and their mothers completed questionnaires at pre- and 6 months post transplant. They also found that QOL had improved 6 months post transplant and emphasized that the pre-SCT levels of family cohesion and child adaptive functioning appeared to be important in QOL and behavioral adjustment.³¹

Other studies have focused on the impact of SCT on QOL, assessed several years later after transplant. Two studies were published in 1995. An Italian group published the results of a study performed in 36 children and adolescents who had received an SCT 1–8 years before. They found that life satisfaction was substantially good, and only 16% complained of physical problems; anxiety and conduct disorders were present mainly in younger subjects and the feeling of depression and inadequacy predominated in older survivors and adolescents.²⁷

In the other study, Kanabar *et al* from St Bartholomew's Hospital in London reported the results obtained from a questionnaire performed in 28 survivors of childhood cancer after megatherapy with autologous bone marrow rescue. In 96%, the overall QOL was judged to be good, 40% had no disabilities, 33% only minimal disabilities and 27% moderate to severe disabilities (mainly pain and depression). Half of the patients expressed certain anxiety about the previous illness.²⁵

In 1997, Kramer *et al* reported the findings of a study in 67 children, the majority under the age of 6 years, performed prior to SCT and at 1 year of follow-up. The objective was to assess the intellectual and adaptive functioning of children receiving an SCT. The majority of

children showed a moderate decline in IQ from base line to 1 year (mean drop was 6 points, from 100 to 94) but no further changes were observed at 3 years. Adaptive functioning dropped significantly at 1 year but, again, no changes were observed between 1 and 3 years of follow-up. The authors concluded that children who undergo HCT are at risk for school difficulties.³²

In 1998, Badell *et al* reported at the meeting of the Pediatric WP in Barcelona the findings of a comparative QOL study performed in 98 adolescents and young adults who had received an SCT at least 3 years before. They found that, compared with a control group of age- and sex-matched healthy subjects, the transplant subjects had a higher QOL satisfaction, fewer problems in social relationship with family and friends, fewer rate of depression and less problems with leisure or spare time but more concerns over studies, work possibilities and physical appearance. In other fields, the rates were similar in both groups.²⁸

Philips *et al* in 2000 evaluated cognitive and academic functioning in 102 children at 1 year and 54 children at 3 years after SCT. The conclusion was that there were no significant changes on global measures of intelligence and academic achievement and no significant differences were observed between patients who had received TBI and those who did not; however, children under 6 years of age at the time of SCT, and particularly those less than 3 years of age, appeared at some risk of cognitive declines.³³

Psychological adjustment after allogeneic SCT was studied and published in 1999 by the group of St Anna's Children's Hospital in Vienna. The subjects were 36 patients aged between 15 and 27 years with an average age of 7 years at transplant and surviving more than 2 years after HCT. The comparative group was formed by bone cancer survivors. The main findings were:²⁶

- Good overall QOL estimate: 5 on a scale of 1–6.
- 85% were able to return to school or employment.
- 35% showed a high level of anxiety.
- 62% felt extremely sensitive and vulnerable.
- 35% showed unfulfilled and strong needs in their love lives.

No differences with the general population were found in family and peer relationships, school performance and self-esteem. The authors concluded that the majority of children who underwent an SCT in their childhood or adolescence demonstrate good QOL but are at risk of developing long-term emotional or social problems.²⁶

More recently, in 2001, Sanders *et al* from the FHCRC in Seattle, reported the findings of a QOL study performed in 120 adult survivors of childhood leukemia who had undergone an HCT, in comparison with 114 treated with chemotherapy alone and with an age- and sex-matched group of 149. Time since treatment was set at 5 or more years (average time: 10 years post transplant). Average age of transplanted group was 27 years and all were over 18 years. The findings in the different domains were as follow:²⁹

- Physical functions: Fatigue and vitality problems present in 6.8% in the SCT group *vs* 3.0% in the chemotherapy group and 2.7% in controls.

- Perception of more limited physical function was superior in HCT survivors.
- Cognitive functions: Chemotherapy survivors had greater difficulties with memory and other cognitive functions compared with SCT survivors and controls.
- Feelings of depression and nervousness were more frequent in chemotherapy survivors.
- Social relationship issues: No differences were found among the three groups in family or friends relationship.
- Health care needs. The SCT survivors reported more illness and physician visits. Diabetes occurred in 10% of SCT group vs 2.6% in CHEMO group and 1.4% in controls.
- Second malignancies were also more frequent in HCT survivors: 8.4 vs 2.6% in chemotherapy group and 1.4% in controls.

In summary, the pediatric HCT survivors reported more illness, physician visits, diabetes and second malignancies than either of the other two groups. They were also lower on physical health scales. Cognitive function problems and depression were greater in the chemotherapy group. Psychosocial factors were equivalent to the comparative subjects.

In 2002, we performed a QOL study in 23 children and adolescents (ages 8–18 years) who had received a BMT as post-consolidation treatment for an AML in first remission. The time since transplant was 3–14 years (median 8 years). The comparative group were 152 healthy age- and sex-matched children.

The method used was the Spanish version of the PEDQOL questionnaire and were evaluated by Dr Calaminus from the University's Children's Hospital of Dusseldorf. In the questionnaire, six domains were assessed through a series of 34 items with answers through a series of 34 items with answers measured with a five-point scale. The assessed domains were physical functioning, autonomy, emotional functioning, cognitive function, social functioning and body image. The proportion of positive and negative answers to specific question in the different groups was compared.³⁴

The analysis of results showed that overall, there were no major differences between groups but children who had received an HCT had a slight decrease in cognitive functions and an increased self-esteem and emotional capacity.³⁵

Summary of findings

- The majority of long survivors enjoy good QOL, return successfully to school or work and do not have problems in social relationships, learning and physical functioning.
- A minority (10–15%) complain of physical problems or present moderate cognitive or psychological dysfunctions.
- Increased emotional capacity may favor the risk of developing long-term emotional problems.
- The importance of family, other social support and psychological adjustments is generally recognized.

- Physical and long-term health-care problems including diabetes are more frequent in recipients of an SCT. However, cognitive and psychological dysfunctions were more frequent among patients who had received longer chemotherapy treatments according to an extensive comparative study.
- More extensive, longitudinal and comparative studies with other alternative therapies are required.

References

- 1 Bathia S, Ramsay NKC, Steinbuch M *et al*. Malignant neoplasms following bone marrow transplantation. *Blood* 1996; **87**: 3633–3639.
- 2 Lowsky R, Lipton J, Fyles G *et al*. Secondary malignancies after bone marrow transplantation in adults. *J Clin Oncol* 1994; **12**: 2187–2192.
- 3 Kolb HJ, Socié G, Duell T *et al*. Malignant neoplasms in long-term survivors of bone marrow transplantation. *Ann Intern Med* 1999; **131**: 738–744.
- 4 Bathia S, Bathia R. Secondary malignancies after hematopoietic cell transplantation. In: KG Blume, SJ Forman, FR Appelbaum (eds). *Thomas Hematopoietic Cell Transplantation*, 3rd edn. Blackwell Publishers: Malden, Mass., 2004, 962–977 (Chapter 70).
- 5 Wheeler C, Khurshid A, Ibrahim J *et al*. Incidence of post-transplantation myelodysplasia/acute leukaemia in non-Hodgkin's lymphoma patients compared with Hodgkin's disease patient undergoing autologous transplantation following cyclophosphamide, carmustine and etoposide. *Leuk Lymphoma* 2001; **40**: 499–509.
- 6 Milligan DW, Ruiz de Elvria MC, Kolb HJ *et al*. Secondary leukemia and myelodysplasia after autografting for lymphoma: results from the EBMT. *Br J Haematol* 1999; **106**: 1020–1027.
- 7 Friedberg JW, Neuberger D, Stone RM *et al*. Outcome of patients with myelodysplastic syndrome after autologous bone marrow transplantation for non-Hodgkin's lymphoma. *J Clin Oncol* 1999; **17**: 3128–3136.
- 8 Curtis RE, Travis LB, Rowlings PA *et al*. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. *Blood* 1999; **94**: 2208–2216.
- 9 Socié G, Curtis RE, Deeg J *et al*. New malignant diseases after allogeneic marrow transplantation for childhood leukemia. *J Clin Oncol* 2000; **18**: 348–357.
- 10 Gerritsen EJA, Stam ED, Hermans J *et al*. Risk factors for developing EBV-related B cell lymphoproliferative disorders after non-HLA-identical BMT in children. *Bone Marrow Transplant* 1996; **18**: 377–382.
- 11 van Esser JW, van Der HB, Meijer E *et al*. Epstein–Barr virus reactivation is a frequent event after allogeneic stem cell transplantation and quantitatively predicts EBV-lymphoproliferative disease following T-cell-depleted SCT. *Blood* 2001; **98**: 972–978.
- 12 Shapiro RS, Chauvenet A, Mc Guire W *et al*. Treatment of B-cell lymphoproliferative disorders with interferon alpha and intravenous gammaglobulin. *N Eng J Med* 1988; **318**: 1334–1335.
- 13 Dotti E, Rambaldi A, Fiocchi R *et al*. Anti-CD20 antibody (ritumab) administration in patients with late occurring lymphomas after solid organ. *Haematologica* 2001; **86**: 618–623.
- 14 Straathof KC, Savoldo B, Heslop HE, Rooney CM. Immunotherapy for post-transplant lymphoproliferative diseases. *Br J Haemat* 2002; **118**: 728–740.

- 15 Faye A, Quartier P, Regerre Y *et al*. Chimaeric anti-CD20 monoclonal antibody (Rituximab) in post-transplant B-lymphoproliferative disorder following stem cell transplantation in children. *Br J Haematol* 2001; **115**: 112–118.
- 16 Rooney LM, Smith CA, Nug CYC *et al*. Use of gene-modified virus-specific T lymphocytes to control Epstein Barr-virus-related lymphoproliferation. *Lancet* 1995; **345**: 9–13.
- 17 Comoli P, Labirio M, Basso S *et al*. Infusion of autologous Epstein–Barr virus (EBV)-specific cytotoxic T cells for prevention of EBV-related lymphoproliferative disorder in solid organ transplant: recipients with evidence of active virus replication. *Blood* 2002; **99**: 2592–2598.
- 18 Curtis SRE, Rowlings PA, Deeg HJ *et al*. Solid cancers after bone marrow transplantation. *N Engl J Med* 1997; **336**: 897–904.
- 19 Deeg H, Socié G. Malignancies after hematopoietic stem cell transplantation: many questions, some answers. *Blood* 1998; **91**: 1833–1844.
- 20 Deeg HJ, Spocié G, Henry-Amar M *et al*. Malignancies after marrow transplantation for aplastic anemia and Fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. *Blood* 1996; **87**: 386–392.
- 21 Favre-Schmuzig G, Hofers S, Passweg S *et al*. Treatment of solid tumors following allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2000; **25**: 895–898.
- 22 Syrjala K. Assessment of quality of life in hematopoietic cell transplantation recipients. In: KG Blume, SJ Forman, FR Appelbaum (eds). *Thomas Hematopoietic Cell Transplantation*, 3rd edn. Blackwell Publishers: Malden, Mass., 2004, 962–977 (Chapter 70).
- 23 Duell S, van Lint MT, Ljungmann P *et al*. Health and functional status of long-term survivors of bone marrow transplantation. *Ann Intern Med* 1997; **126**: 184–192.
- 24 Bush NE, Donaldson GN, Haberman MH *et al*. Conditional quality of life after hematopoietic stem cell transplantation: a longitudinal follow-up of 415 patients. *Biol Blood Marrow Transplant* 2000; **6**: 576–591.
- 25 Kanabar DJ, Attard-Montalto S, Saha V *et al*. Quality of life in survivors of childhood cancer after megatherapy with autologous bone marrow rescue. *Ped Hematol Oncol* 1995; **12**: 29–36.
- 26 Felder-Puig R, Peters C, Matthers-Martin S *et al*. Psychosocial adjustment of pediatric patients after allogeneic stem cell transplantation. *Bone Marrow Transplant* 1999; **24**: 75–80.
- 27 Nespoli L, Verri AP, Locatelli F *et al*. The impact of pediatric bone marrow transplantation on quality of life. *Qual Life Res* 1995; **4**: 233–240.
- 28 Badell I, Igual L, Gómez P *et al*. Quality of life in young adults having received a BMT during childhood: a GETMON study. *Bone Marrow Transplant* 1998; **21** (Suppl. 2): S68–S71.
- 29 Sanders JE, Syrkala KL, Hoffmister PH *et al*. Quality of life of adult survivors of childhood leukemia treated with chemotherapy or bone marrow transplant. *Blood* 2001; **98**: 741a–742a.
- 30 Phipps S, Dunavant M, Garvie PA *et al*. Acute health-related quality of life in children undergoing stem-cell transplants. I-Descriptive outcomes. II Medical and demographic determinants. *Bone Marrow Transplant* 2002; **29**: 425–442.
- 31 Barrera M, Boyd-Pringle LA, Sumbler K, Saunders S. Quality of life and behavioural adjustment after pediatric bone marrow transplantation. *Bone Marrow Transplant* 2000; **26**: 427–435.
- 32 Kramer JH, Crittenden MR, De Santes H, Cowan MJ. Cognitive and adaptive behavior 1 and 3 years following bone marrow transplantation. *Bone Marrow Transplant* 1997; **19**: 607–613.
- 33 Phipps S, Dunavant M, Srivastave DK *et al*. Cognitive and academic functioning in survivors of pediatric bone marrow transplantation. *J Clin Oncol* 2000; **18**: 1004–1011.
- 34 Calaminus G, Weinspach S, Teske C, Göbel U. Quality of life in children and adolescents with cancer. *Klin Pädiatr* 2000; **212**: 211–215.
- 35 Ortega JJ, Díaz de Heredia C, Olivé T *et al*. Allogeneic and autologous stem cell transplantation for AML in first remission: long-term results, late effects and quality of life. *Pediatr Blood Cancer* 2004; **43**: 375 (Abstract).