

## Secondary malignancies after hematopoietic stem cell transplantation

### Minireview

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Hematopoietic stem cell transplantation (HSCT) offers patients with malignant and nonmalignant diseases the opportunity to pursue life-prolonging therapy. The number of survivors after successful HSCT is continually increasing. However, HSCT can induce tissue and organ damage that occurs not only “on treatment”, but long after completing therapy. Secondary malignancies belong to serious late complications after HSCT. A significant association of certain risk factors with increased likelihood of secondary malignancies after HSCT has been published over the last ten years. Better knowledge of pathogenesis of these complications, their early identification and treatment may contribute to better health outcomes of allogeneic and autologous hematopoietic stem cell transplantation recipients. We review here the incidence and risk factors of secondary malignancies after hematopoietic stem cell transplantation.

*Key words: hematopoietic stem cell transplantation, late complications, secondary malignancies*

Hematopoietic stem cell transplantation (HSCT) is widely used in the treatment of malignant and nonmalignant diseases. The number of survivors after successful HSCT is increasing. Attention is now being focused not only on acute but also late effects of this treatment appearing long after completing HSCT [1]. The development of secondary malignancies is recognized as one of the most serious complications in HSCT recipients and the incidence is an eight-fold higher than the incidence expected in the general population [2]. HSCT recipients are at increased risk for secondary malignancies because of several risk factors: radiotherapy and chemotherapy used for treatment of the primary malignant disease and as a part of pretransplantation conditioning, immunodeficiency due to delayed and incomplete recovery of the immune system,

immune system alterations by the graft versus host disease (GVHD), and immunosuppressive therapy for GVHD.

Secondary malignancies after HSCT are divided into three general categories:

- post-transplant lymphoproliferative disorder (PTLD),
- hematologic malignancies (primarily therapy-related myelodysplastic syndrome and acute myeloid leukemia)
- solid tumors.

The risk of PTLD and hematologic malignancies is increasing with time from HSCT and plateaus 10 years post-HSCT, whereas the risk of solid tumors continues to increase even 20 years after transplant [2].

Here, we review the incidence and risk factors of secondary malignancies after hematopoietic stem cell transplantation.

### 1. Lymphoproliferative disorders

Post-transplant lymphoproliferative disorder (PTLD) is a life-threatening complication after transplantation. The recently updated World Health Organization classification defined PTLD as a lymphoid proliferation or lymphoma that develops as a consequence of immunosuppression in

Abbreviations: HSCT – hematopoietic stem cell transplantation, GVHD – graft versus host disease, PTLD – post-transplant lymphoproliferative disorder, EBV – Epstein Barr virus, t-MDS/AML – therapy-related myelodysplastic syndrome and acute myeloid leukemia, TBI – total body irradiation, ASCT – autologous hematopoietic stem cell transplantation, PBSC – peripheral blood stem cells, SCC – squamous cell carcinoma, BCC – basal cell carcinoma, nSCC – non-squamous cell carcinoma

a recipient of a solid organ or bone marrow allotransplantation. According to histopathological heterogeneity PTLD is classified into four major categories: 1) early lesions, comprising reactive plasmocytic hyperplasia and mononucleosis-like forms; 2) polymorphic PTLD (polyclonal or monoclonal); 3) monomorphic PTLD, including lymphomas and multiple myelomas, mostly non-Hodgkin's lymphoma of B-cell origin; and 4) classic Hodgkin's lymphoma-type PTLD [3 – 5].

The Epstein Barr virus (EBV) plays an important role in the pathogenesis. PTLD results from the outgrowth of EBV-infected B cells that would normally be controlled by an effective EBV-specific cytotoxic T-cell (CTL) response [6]. The importance of T-cell dysfunction in the pathogenesis of PTLD is highlighted by the fact that the majority of PTLD cases occur within the first year post-transplant, before reconstitution of the EBV-specific CTL response, when the recipient is severely immunocompromised to prevent graft versus host disease (GVHD) or graft rejection [7].

PTLD may present in several ways; signs and symptoms similar to those seen during primary EBV infection and include fever, sweats, generalized malaise, enlarged tonsils, and cervical lymphadenopathy. PTLD may also present as involvement of other organs, including EBV-associated enteritis with multiple ulcers [8, 9], EBV-related hepatitis [10], pulmonary involvement [11], involvement of the central nervous system [12], and fulminant EBV – associated hemophagocytosis [13]. Often, diffuse disease is diagnosed only at autopsy in patients thought to have fulminant sepsis or severe GVHD [7].

Mortality rates were reported to be as high as 50-90% [14 – 16]. The incidence of PTLD varies from 1% to 20% based on the organ transplanted [17]. LANDGREN et al evaluated 26 901 patients from 271 centers. In this largest multinational study they found, that PTLD developed in 127 recipients, with 105 (83%) cases occurring within 1 year after transplantation [18].

The strongest risk factor for PTLD were T-cell depletion of donor marrow, and use of antithymocyte globulin (ATG) for prophylaxis or treatment of GVHD. Methods of selective T-cell depletion were associated with an 8- to 15-fold increased risk of PTLD compared with methods that removed both T and B cells (such as anti-CD52 monoclonal antibody). The development of acute or chronic GVHD, or both, resulted in a less pronounced 2-fold increase in PTLD risk [18]. Patients who received a transplant from HLA mismatched related or unrelated donors had significantly higher risk for PTLD. The incidence of PTLD was 0.3% (1/327) in HLA matched related HSCT patients, 3.4% (7/208) in haploidentical HSCT patients and 2.3% in unrelated HSCT patients [19]. The incidence of PTLD after allogeneic umbilical cord blood transplant is <2% [20], and it has only been described in rare cases [21]. There was recent report about increased risk of PTLD in older patients aged 50 years or more at transplantation and with second transplantation [18]. More intensive immunosuppression regimens following reduced intensity conditioning result in an increased incidence of PTLD [22].

The establishment of early diagnosis and treatment in the management of PTLD is very important. Radiology studies may reveal extensive mass only [23]. It seems adequate to recommend that patients identified at high-risk for PTLD should be monitored with EBV viral load measurements [24, 25]. Patients with 2 or more major risk factors for PTLD development or with EBV loads over  $10^6$  copies/ml, especially lasting over two weeks, appear to have an increased risk for PTLD, and pre-emptive therapy may be of clinical utility [26]. Today the most frequently used pre-emptive therapy for EBV infection post transplant is the administration of rituximab [27, 28]. MOOSMANN et al and HESLOP et al reported effective and long-term control of EBV PTLD after the infusion of small numbers of directly isolated EBV-specific T cells [29, 30]. Reduction of immunosuppression, donor lymphocyte infusion, chemotherapy, or use of antiviral agents has at best a limited place in the management of PTLD [27].

## 2. Hematologic malignancies

Patients after hematopoietic stem cell transplantation have a significant risk of therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/AML). Secondary leukemia refers to the appearance of a new, biologically-unrelated leukemia different from the primary malignancy and usually follows autologous HSCT and not allogeneic transplants. The incidence of these disorders is rising because of improved primary malignancy outcomes. In studies the cumulative incidence of t-MDS/AML was 1,4% at 20 years, with plateau occurring by 10 years after allo- or autotransplant [2] and 6,8% at 10 years [31] up to 19,8% with at least 5 years of follow-up after autologous transplantation for lymphoma [32]. The prognosis of t-MDS/AML is very poor, with a median survival of 6-12 months [33, 34].

Risk factors for development of t-MDS/AML after hematopoietic stem cell transplantation (HSCT) have been suggested by several studies. The most important factor is prior chemotherapy. There are two different syndromes: one that occurs after exposure to alkylating agents with a long latency (5-8 years), frequently preceded by an MDS phase and is associated with high risk karyotypes such as abnormalities of chromosomes 5 and/or 7 [35]. The second syndrome follows the use of topoisomerase II inhibitors, has a short latency period (1-3 years), without antecedent dysplastic phase and with abnormalities of chromosome 11q23 or 21q22 [36].

Transplantation-conditioning regimens including total body irradiation (TBI) at doses 12 Gy or less did not appear to elevate leukemia risk compared with non-TBI regimens, however, a statistically significant increased risk was found for TBI doses of 13,2 Gy [37]. MICALLEF et al and HOSING et al reported similar findings [38, 39]. KALAYCIO et al implicated local, subtotal radiation therapy administered before autologous HSCT (ASCT) as a risk factor for t-MDS/AML in contrast to ARMITAGE et al, who concluded that pre-ACST

exposure to radiation does not significantly increase the risk of t-MDS/AML after ASCT for lymphoma [31, 40].

Secondary leukemia occurring after HSCT for AML is rare [41]. CHO et al reported a case of the second de novo acute myeloid leukemia following allogeneic HSCT for a first occurrence of AML [42]. Most reports of secondary leukemia follow ASCT for lymphoma and the risk was higher in patients who received peripheral-blood stem cells (PBSC) as their stem cell source [2, 43]. It can be explained by finding that the cells are harvested in a state of incomplete DNA repair after cytotoxic chemotherapy and then the PBSC product will be contaminated with a higher percentage of damaged cells that are already preleukemic due to prior chemotherapy [2]. KALAYCIO et al showed that difficulty in harvesting PBSC for ASCT is an independent risk factor for t-MDS/AML [31].

An increased risk of t-MDS/AML has also been seen in patients following ASCT performed for breast cancer, multiple myeloma and germ cell tumors, but this risk is lower than in patients with lymphoma [44, 45]. The risk has been shown to increase with patient age (more than 40 years) [46, 47].

In addition, there is a number of recent studies suggesting that inherited polymorphisms in genes governing drug metabolism, DNA repair and leukemogenesis may determine the risk of t-MDS/AML [48, 49]. In a recent study, CHAKRABORTY et al reported significant alteration in telomere dynamics in hematopoietic cells preceding the development of t-MDS/AML and these telomere alterations were independent of other known risk factors associated with development of t-MDS/AML on multivariate analysis. Telomere shortening may reflect increased clonal proliferation or altered telomere regulation in premalignant cells, and the resultant genetic instability associated with shortened telomeres may contribute to leukemic transformation in t-MDS/AML after HSCT [50]. HAKE et al

therefore hypothesize that the mechanism of t-MDS/AML following HSCT is multifactorial, involving 1) genotoxic stress due to chemoradiotherapy administered before ASCT and advancing age, 2) proliferative stress associated with engraftment and 3) inherited polymorphisms in genes governing drug metabolism, DNA repair and leukemogenesis [51].

The detection and prevention of t-MDS/AML can be improved by identification of high risk patients and careful selecting patients for ASCT, minimizing the exposure to leukemogenic agents before stem cell collection and analyzing the inherited genetic polymorphisms. It is reasonable to recommend close monitoring of blood counts during the first 5 years after autologous transplantation. A high-index of suspicion should be present for unexplained pancytopenias. These should be investigated thoroughly with bone marrow biopsy, and cytogenetic and molecular studies for markers of myelodysplastic syndromes [39].

Therapy-related myelodysplastic syndromes and acute myeloid leukemia have a poor prognosis with conventional therapy. Allogeneic HSCT can cure patients with t-MDS/AML and its results have markedly improved over time. Not being in complete remission at the time of transplantation, abnormal intermediate or high risk cytogenetics and higher age of the patients are the most significant factors predicting worse survival [52, 53]. Future progress for these patients will depend on discovering new noncarcinogenic therapies for the treatment of primary disorders and developing more effective and safer therapies for t-AML and t-MDS [54].

### 3. Solid tumors

Survivors of HSCT have a life-long increased risk of solid cancers incidence. The overall incidence is 2-fold higher than

**Table 1. Incidence and risk factors of solid tumors after hematopoietic stem cell transplantation**

<i>Author, year</i>	<i>No. of HSCT</i>	<i>No. of solid tumors</i>	<i>Incidence (years)</i>	<i>RR</i>	<i>Major sites (number of cases)</i>	<i>Risk factors</i>
Bhatia et al., 2001 [56]	2129	29	6,1% (10 years)	1,3	Skin (9), thyroid (2), oral (6), liver (2), cervix (2), breast (2)	TBI, cGVHD
Baker et al., 2003 [2]	3372	62	3,8% (20 years)	2,8	Skin (19), brain (4), thyroid (1), melanoma (8), oral (1), lung (1), sarcoma (6), breast (4)	Old age
Au et al., 2004 [57]	605	9	6,4% (5 years)	4,5	Liver (2), oral (3), breast (1), lung (1), ovarian (1), gastric (1)	Nil
Hasegawa et al., 2005 [58]	557	31	4,2% (10 years) 6,17% (15 years)	5,13	Skin (9), oral (7), breast (4), other (11)	Old age
Shimada et al., 2005 [59]	809	19	1,9% (5 years) 4,2% (10 years)	2,82	Oral (7), GIT (6), breast (1), cervix (2), uterine corpus (1)	cGVHD, old age
Gallagher et al., 2007 [60]	926	30	3,1% (10 years)	1,85	Skin (12), oral (5), lung (5), colon (2), bladder (2), breast (1), kidney (1), vulva in situ (1), primary unknown (1)	Woman donor, old age
Rizzo et al., 2009 [55]	28 874	189	2,5% (10 years) 5,8% (15 years) 8,8% (20 years)	2,09	Oral (27), melanoma (18), brain (18), thyroid (16), bones (6), soft tissue (7), liver (7), breast (13)	Radiation, cGVHD, young age, male sex

HSCT – hematopoietic stem cell transplantation, TBI – total body irradiation, cGVHD – chronic graft versus host disease, RR – relative risk

that expected in the general population and the risk reached 3-fold among patients followed for 15 years or more after transplantation [55]. The cumulative incidence ranges from 2% to 6% at 10 years after transplantation (Tab 1). Among 3-year survivors, the cumulative incidence was 7% for bone marrow and 16% for peripheral-blood recipients [61]. An increasing number of cases of donor-derived solid malignancies has been reported [62].

Several factors contribute to the development of solid cancers: total body irradiation (TBI) and chemotherapy as part of the conditioning regimens, pretransplantation therapy, primary disease, age, immune dysfunction (T-cell depletion, HLA mismatched allo-HSCT, chronic graft versus host disease (GVHD) and immunosuppressive therapy) (Tab 1). The most frequent malignant diseases were neoplasms of the skin, oral cavity, thyroid gland, bone, uterus, liver, breast and glial tissue (Tab 1).

The most frequent solid cancers are squamous cell carcinomas (SCC) [63]. The most common localization of SCC was the skin, genitourinary tract (cervix, vagina, and vulva) and oral cavity (tongue, salivary gland) [64]. Premalignant changes of the oral mucosa were mucositis, xerostomia, and lichenoid changes, developing into erosive forms [65]. The risk of SCC was related to chronic GVHD and male sex [55, 66].

Leisenring et al reported in a cohort of 4810 recipients of allogeneic HSCT, that acute GVHD increased the risk of SCC, whereas chronic GVHD increased the risk of both basal cell carcinoma (BCC) and SCC. There were 158 patients who developed at least one BCC at a median of 7,9 years after HSCT and at a median age of 47,9 years. Ninety-five patients developed SCC at a median of 6,3 years after HSCT and at a median age of 48,9 years. A total of 58 patients had more than one occurrence of non-melanoma skin or mucosal cancer. The risk of BCC was increased when more than 15 years had passed since HSCT, whereas the risk of SCC was increased in patients with a follow-up time of more than 20 years [64]. TBI was a risk factor for the development of BCC for those exposed at young ages and there was no significant increase in BCC risk among patients treated after age 40 years [67].

CAVALIER et al reported several patients who developed skin cancer over a period of 2-26 months after nonmyeloablative HSCT. This finding suggests that even nonmyeloablative conditioning regimen and relatively short-term immunosuppression does not eliminate skin cancer risk in the post transplantation period [68].

Patients with Fanconi anemia after HSCT have a 4-fold increased risk of developing head and neck squamous cell carcinoma associated with a very poor prognosis [69]. MASSE-ROT et al concluded, that a very important attempt should be made to prevent this cancer by reducing chronic GVHD and using conditioning without irradiation [70].

In the largest study to date, RIZZO et al studied a multi-institutional cohort of 28 874 allogeneic transplant recipients with 189 solid malignancies. TBI was a significant risk factor for non-squamous cell carcinomas (nSCC), particularly can-

cers of the brain and central nervous system (CNS), breast, thyroid, bone and connective tissue, and melanoma. They found a strong association of previous cranial irradiation and younger age with increased risk of CNS cancers. It has been reported that the risk of developing secondary brain and CNS tumors in HSCT recipients is 5.94:1 (observed:expected cases). The time since transplantation to development of these tumors ranges from 5 to 9 years [55]. The commonest CNS tumors included glioblastoma multiforme, astrocytoma and primitive neuroectodermal tumor [71]. PANIGRAHI et al reported a case of malignant oligoastrocytoma that developed 7 years following matched unrelated bone marrow transplantation in a child with acute myeloid leukemia [72].

Female survivors of allogeneic HSCT are at increased risk of breast cancer. FRIEDMAN et al evaluated 3337 female 5-year survivors of allogeneic HSCT. Fifty-two recipients developed breast cancer at a median of 12,5 years following HSCT, at a median age of 47,5 years. Cumulative incidence markedly increased from 10 years to 20 years after HSCT. At 25 years the cumulative incidence was 11%, higher among survivors who had been treated with TBI than those who did not receive TBI. Patients younger than 18 years had the highest risk [73].

Radiation to the neck and TBI are associated with dose-related increases in risk of thyroid malignancy, often with a long latent period [74]. Thyroid tumors occurred at a median of 9.9 (4.5-22.3) years after HSCT [75]. In the largest retrospective multicenter survey with more than 70 000 HSCT recipients, COHEN et al reported that HSCT recipients were at significantly higher risk of secondary thyroid cancer than the general population, with a ratio of observed to expected cases of 3.26 [76]. In a recent report of second malignancies following HSCT for acute leukemia, five thyroid carcinomas occurred among 3182 children with a strong relationship between age of transplant and the occurrence of thyroid cancer [71]. The most common types of thyroid cancer are thyroid adenomas and papillary carcinomas [75, 77].

Patients at risk for secondary malignancy should be encouraged to perform self-examination such as breast, oral cavity and skin examination, and to avoid high-risk behaviors such as smoking, alcohol consumption or excessive unprotected skin UV exposure. Life-long clinical assessment in yearly intervals should include symptom review, clinical examination and screening testing for secondary malignancies. Some experts recommend initiation of screening mammography earlier than age 40 for women with radiation exposure [78].

## Conclusion

Over the last years, the treatment results of stem cell transplantation have improved. An increased number of patients are becoming long-term survivors following hematopoietic stem cell transplantation. The development of secondary malignancies belongs to serious life-threatening complications of this therapy. The latest research published in last decade has shown

that the incidence of these late complications continue to rise the longer the follow-up is. Better understanding the pathogenetic mechanisms of late complications that can occur after HSCT and knowing of risk factors associated with increased likelihood of secondary malignancies provides a basis for optimal surveillance and early intervention.

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