Journal of Cancer Research and Practice

journal homepage: https://journals.lww.com/jcrp

Original Article

Second Primary Malignancy after Hematopoietic Stem Cell Transplantation: A Single Institute Experience

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Abstract

Background: Hematopoietic stem cell transplantation (HCT) is a curative treatment for various hematologic malignancies and some benign hematologic diseases. However, in addition to chronic graft-versus-host disease, second primary malignancy is also a long-term adverse effect. **Materials and Methods:** We retrospectively collected long-term follow-up data of 380 patients who had undergone transplantation (autologous in 184 with 126 long-term survivors and allogeneic in 196 patients with 100 long-term survivors) between 2001 and 2021 and analyzed the incidence and types of second primary malignancy. **Results:** Twelve patients had second primary malignancy, including five with head-and-neck squamous cell carcinoma (SCC), three with myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), one with acute lymphoblastic leukemia (ALL), one with esophageal SCC, one with breast cancer, and one with papillary thyroid cancer. Of eight patients who underwent allogeneic hematopoietic stem cell transplants, five had head and neck, one had esophageal, one had breast, and one had papillary thyroid cancer. Of four patients who underwent autologous transplants, three had MDS/AML, and one had ALL. The cumulative incidence of second malignancy was 6% at 10 years and 16% at 19 years, and the postautologous and postallogeneic transplant rates were 5% versus 7% at 10 years and 15% versus 17% at 19 years. **Conclusion:** The occurrence of a second malignancy after HCT is a crucial issue of concern, and an early diagnosis is essential for posttransplant patients.

Keywords: Hematopoietic stem cell transplant, posttransplant second malignancies, second primary malignancy

Introduction

Hematopoietic stem cell transplantation (HCT) is a curative treatment for malignant and nonmalignant hematologic diseases. Autologous hematopoietic stem cell transplant is the standard recommendation for sensitive relapsed lymphoma and frontline settings in some cases of high-risk lymphoma or multiple myeloma. Allogeneic transplant is thus one of the curative options for acute myeloid or lymphoblastic leukemia, high- or intermediate-to-high-risk myelodysplastic syndrome, relapsed refractory aggressive lymphoma or myeloma, and also nonmalignant hematologic diseases such as severe aplastic anemia or other bone marrow failure syndromes. However,

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Submitted: 24-Dec-2023 **Revised:** 06-Apr-2024
Accepted: 06-May-2024 **Published:** 26-Jun-2024

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jcrp

DOI: 10.4103/ejcrp.eJCRP-D-23-00054

How to cite this article: Tan TD, Chiou LW. Second primary malignancy after hematopoietic stem cell transplantation: A single institute experience. J Cancer Res Pract 2024;11:67-72.

in long-term survivorship, the second primary malignancy adversely affects survival.[1]

In the setting of hematopoietic stem cell transplant, the primary causes of second malignancies include high-dose chemotherapy, total body irradiation (TBI), the dose and fields of radiation, severity and duration of immune compromise, extent of chronic graft-versus-host disease (GVHD), and Epstein–Barr virus (EBV) infection. High-dose chemotherapy, especially alkylating agents, and ionizing radiation can damage DNA and result in leukemogenesis.[2,3] Primary immunodeficiencies frequently associated with cancer include common variable immunodeficiency, Wiskott–Aldrich syndrome, ataxia-telangiectasia, and severe combined immunodeficiency. The increased incidence of cancer has been attributed to the defective elimination of altered or transformed cells and impaired immunity toward cancer cells.[4] The Center of International Bone Marrow Transplant Registry (CIBMTR) reported that the significant risk factors for the development of squamous cell carcinoma (SCC) after allogeneic HCT were a long duration of chronic GVHD therapy, the use of azathioprine (particularly when combined with cyclosporin) and steroids, and severity of chronic GVHD.[5]

Materials and Methods

We searched the database of our institute for patients with second cancers after autologous and allogeneic HCT between 2001 and 2021. Data collection was stopped after February 2022, and the median follow-up period was 7.7 years. We wanted to delineate our real-world experience of the incidence, cancer type, time of occurrence, and outcomes of salvage treatment in these patients.

Every patient to undergo HCT has signed the informed consent form. This retrospective data collection is approved by our Institute Review Board Committee of Koo Foundation Sun Yat-Sen Cancer Center. (KFSYSCC-IRB No./Protocol No.: 20221110A); 125, Lih-Der Road, Pei-Tou District, Taipei, Taiwan. Phone: +886-2-28970011 Fax: +886-2-28974141.

Results

We identified 380 patients between 2001 and 2021. Of these patients, 184 underwent autotransplant and 196 underwent allotransplants, with long-term survival rates of 68% (126/184) in the autologous group and 51% (100/196) in the allogeneic group [Table 1]. Twelve patients had second primary malignancies, including 5 with head-and-neck SCC, three with myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), one with acute lymphoblastic leukemia (ALL), one with esophageal SCC, one with breast cancer, and one with papillary thyroid cancer [Table 2]. Of these 12 patients (6 females and 6 males), the median age at the primary malignancy diagnosis was 41.83 (range: 18–56) years. The cumulative occurrence of second primary malignancies in our long-term survival patients was 6% at 10 years and 16% at 19 years [Figure 1], including 5% versus 7% at 10 years and 15% versus 17% at 19 years after autologous and allogeneic HCT, respectively [Figure 2], with a range between 33 and 199 months.

Treatment of the second primary malignancy included surgery with or without adjuvant radiation in five of the head-and-neck SCC patients and one esophageal cancer patient. Systemic chemotherapy with or without allogeneic HCT was performed in three MDS/AML patients and one bi-phenotypic ALL patient. The breast cancer patient underwent surgery, postoperative adjuvant chemotherapy, and radiation. The papillary thyroid cancer patient underwent thyroidectomy and iodine 131 radioablation and was disease-free for over 134 months [Table 2].

Of the six SCC patients, four were disease-free after surgery, but one died after receiving a COVID-19 vaccination. Two patients died of second cancer progression. In four of the MDS/AML and ALL patients, two were leukemia free after intensive chemotherapy and salvage allogeneic HCT, one low-risk MDS patient was under regular follow-up without treatment for over 100 months, and one AML patient died of leukemia relapse even after allogeneic transplant. The other two patients with breast cancer and papillary thyroid cancer were disease free after surgery and adjuvant therapy for over 54 months and 134 months, respectively.

Table 1: The disposition of the patients undergoing hematopoietic stem cell transplantation between 2001 and 2021

Age	40.8 y (mean); 44.7 (median; (range 1.6~66.7)
<18 y	34 (9%)
<19 y	224 (59%)
<20 y	118 (31%)
<21 y	4 (1%)
Sex	M 57%/F 43%
Diseasess	
Lymphoma	152 (40%)
Hodgkin	25
Non-Hodgkin	127
Leukemia	144 (38%)
AML	73
ALL	30
CML	4
CLL	1
Other leukemia	36
Myeloma	41 (11%)
Other	43 (11%)
Transplant	380 (100%)
Autologous	184 (48%)
Allogeneic	196 (52%)
MRD	108 (29%)
MUD	57 (15%)
Haploidentical	23 (6%)
Cord blood	8 (2%)

AML:acute myeloid leukemia;ALL: acute lymphoblastic leukemia

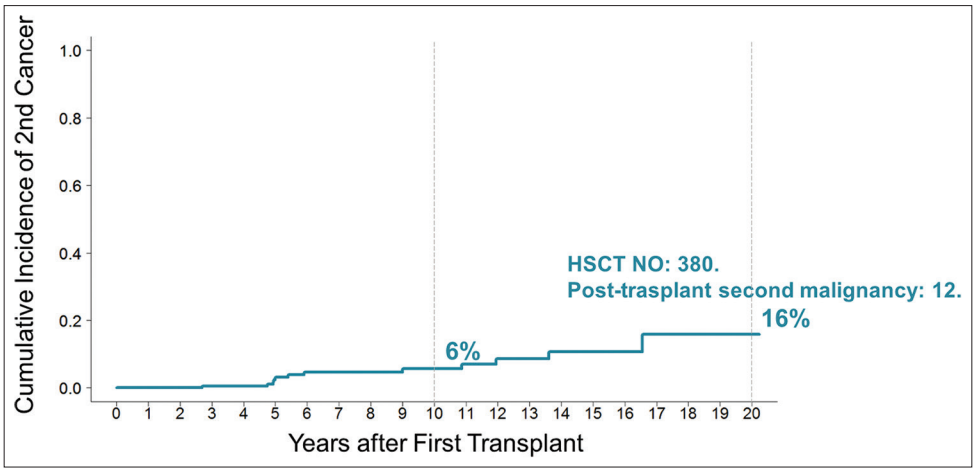

Figure 1: The cumulative occurrence of second malignancies after hematopoietic stem cell transplantation between 2001 and 2021

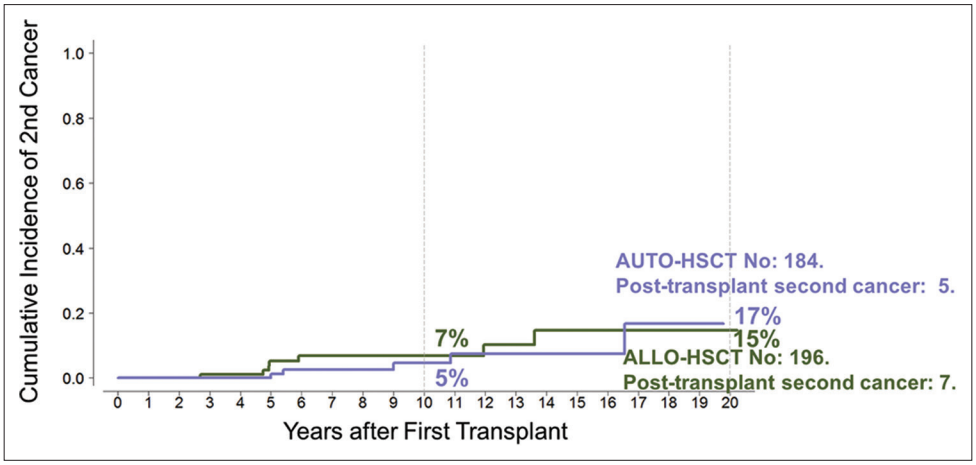

Figure 2: The occurrence of second malignancies after hematopoietic stem cell transplantation between 2001 and 2021 – Auto- versus allo-transplant

Discussion

In this study, we did not include patients with posttransplant lymphoproliferative disorders, which are EBV related and treated with rituximab with or without chemotherapy. Of the 380 patients in this study, 12 had second primary malignancies. The cumulative incidence was 6% at 10 years and 16% at 19 years, including 5% versus 7% at 10 years and 15% versus 17% at 19 years after autologous and allogeneic HCT, respectively, which is higher than reported in a previous large-scale study of the CIBMTR database.[6,7] Both results show that the observed-to-expected ratio increased with time after transplantation and that a predisposing factor for squamous cell cancers included chronic GVHD. However, none of our patients had malignant melanoma, which may be due to ethnic differences. In their 28,874 recipients, the cumulative incidence of new solid cancers was 1% at 10 years, 2.2% at 15 years, and 3.3% at 20 years after transplantation. However, in our small cohort, the rates were 7% and 17% at 10 and 19 years after allogeneic transplants, respectively. A single-institution review of 4905 survivors of allogeneic hematopoietic cell transplant from Seattle reported 581 secondary cancers in 499 individuals after a median follow-up of over 12 years.[3] The cumulative incidence of secondary malignant neoplasms at 30 years after HCT for the entire cohort was 22.0%. At 20 years post-HCT, the cumulative incidence rates were 8.1%, 13.5%, and 23.6% for patients younger than 20 years of age, 20–50 years, and older than 50 years, respectively, which is similar to our cohort. In an Italian multicenter study including a total of 1347 patients with aggressive lymphoma after high-dose chemotherapy and autologous HCT at a median follow-up of 7 years, the cumulative incidence at 10 years of secondary myelodysplasia/acute leukemia (sMDS/AL) was 4.52%,[2] similar to 5% at 10 years and 15% at 19 years in our series.

Six of our 100 survivors in the allogeneic hematopoietic stem cell transplant cohort developed upper aerodigestive tract SCC (5 with head and neck and 1 with esophageal cancer), all of whom had posttransplant extensive chronic GVHD presenting as prolonged oral mucositis with thrush or leukoplakia, and the median occurrence of second SCC was 84.5 months after allo-HCT. Two patients died due to secondary refractory disease, and four were disease free after surgery and local irradiation. However, one of the second

Table 2: Second cancer occurrence after hematopoietic stem cell transplantation

Patients number	Age	Sex	Primary Maligancy	Date of Primary Mlignancy	Primary Tx	Type of HCT	Date of HCT	Type of Second Malignancy	Date of Second Maligancny	Post-transplant Second Malignancy	Tx of Second Malignancy	Outcome
No 1	38	F	CLL	10-03-2003	chlorambucil, R-COP, FC	Allo-HSCT from MSD	29-07-2009	Papillary thyroid	09-04-2012	33 m	Thyroidectomy + radioisotope	Disease-free
No 2	18	M	T-Lymphoblastic lymphoma	02-04-2004	GMALL	Auto-HSCT	29-09-2004	MDS/AML	21-04-2021	16y7m	Chemotherapy and then MUD allo-HCT	Relapsed and resistant then died of AML relapse
No 3	42	M	FL with large cell transformation	11-11-2004	RT, CHOP, R-ICE, fludarbine	Allo-HSCT from MSD	18-06-2008	Oral and palatal cancer	29-05-2020	11y11m	surgery	Disease-free
No 4	43	F	FL grade III	06-03-2006	R-CHOP, R-ICE	Auto-HSCT	09-09-2009	MDS RA,46, XX, del (20)(q13.1)	04-02-2015	5Y5M	Watchful observation	Stable disease without treatment
No 5	46	M	IgGkappa MYELOMA, stage III	01-06-2009	Td	Auto-HSCT	07-05-2010	MDS/AML inv3	07-05-2019	9y0m	Chemotherapy and MSD allo-HCT	Disease-free
No 6	48	M	AML	01-02-2013	I3A7 -> HiDAC	Allo-HSCT from MUD	11-09-2013	Esophageal cancer	08-08-2019	5y11m	CCRT, chemotherapy, RT, PD-1 inh	Died on 2021/05/12 because of esophageal cancer in progression
No 7	47	M	AML	31-08-2011	I3A7	Allo-HSCT from MUD	06-03-2012	Hypopharyngeal cancer	30-11-2016	4y8m	palliative care	Died on 2017/03/26 because of tongue cancer in progression
No 8	52	F	Extra-nodal NK/T cell lymphoma, nasal type	28-03-2011	ICE -->SMILE	Allo-HSCT from MUD	19-04-2013	Tongue SCC	26-03-2018	4y10m	Left partial glossectomy	Disease-free
No 9	49	F	AML	02-07-2015	I3A7 -> HiDAC	Allo-HSCT from MSD	23-12-2015	Right palate squamous cell carcinoma	30-11-2020	4y11m	wide excision	Disease-free
No 10	56	F	Myeloma	24-07-2013	VTd	Auto-HSCT	21-02-2014	Acute biphenotypeic lymphoblastic leukemia, del 3,7,9,13	19-02-2019	5y0m	Chemotherapy	Disease-free
No 11	21	F	Acute lymphoblastic leukemia	31-01-1999	GMALL	Allo-HSCT from MUD	18-05-2005	Breast cancer (family history+)	28-12-2018	13y7m	Surgery, chemotherapy, and radiation	Disease-free
No 12	42	M	Myeloma	30-03-2007	VAD	Allo-HSCT from MSD	11-02-2009	Hypopharyngeal cancer	22-02-2019	10y0m	Hypophary ngectomy	Disease-free but died of post-vaccintion for COVID-19

cancer-free patients died after administration of the Moderna COVID-19 vaccination. The possibility of head-and-neck cancer should be suspected in patients with nonhealing oral lesions, leukoplakia, localized oral pain, or changes in the mucosal color or texture, and screening for these patients is mandatory. Because of the small number of patients in our series, we cannot provide a definitive statistical difference between the severity of chronic GVHD in our patients with and without a second malignancy. However, in an international case–control study of over 24,000 patients, chronic GVHD and its therapy were strongly related to the risk of SCC, whereas no increased risk was found for non-SCCs. Major risk factors for developing SCC were a long duration of chronic GVHD therapy, the use of azathioprine (particularly when combined with cyclosporine) and steroids, and severe chronic GVHD.[5] In our cohort, the patients with subsequent upper aerodigestive tract SCC had more extensive chronic GVHD and more extended use of immunosuppressants, including cyclosporine and corticosteroids, consistent with the previous literature. We did not check the genetic origin of SCC in either the donor or host; however, in one study of oral SCCs arising in long-term survivors of allogeneic HCT, the source of the malignant cells was the HCT donor in four of the eight cases.[8] Therefore, clinical screening of oral and esophageal cancer (e.g., head-and-neck surgeon examinations every 6 months and esophagi-gastroscopy every year) is mandatory among patients exposed to persistent chronic GVHD, prolonged immunosuppressive therapy, or both. In this retrospective review, the current study includes a lack of detailed information on the family history of cancer and exposure to well-known risk factors for malignancies, such as smoking, alcohol consumption, drug abuse, chemical exposure, and health-related lifestyles.

According to a report from the FHCRC and EBMT-late Effect Working Party,[9] 52 in of 3337 survivors developed breast cancer at a median of 12.5 (range: 5.7–24.8) years following HCT. The 25-year cumulative incidence was 11.0% and was higher among survivors who received TBI (17%) than in those who did not receive TBI (3%). In multivariable analysis, the increased risk was associated with a longer time since transplantation (20 + years after transplantation), receiving TBI, and younger age at transplantation (HCT < 18 years). One of our allogeneic transplant cohorts developed breast cancer. This patient had ALL at the age of 21 years, underwent allo-HCT from MUD at the age of 24 years on CR2 with BuCy conditioning (busulfan and cyclophosphamide) plus ATG, cyclosporine, and MTX as GVHD prophylaxis, and was found to have second breast cancer at the age of 38 years (13 years and 7 months after allo-HCT). She remained disease free after surgery, chemotherapy, and radiation. According to our experience and the literature review, we conclude that female survivors of allogeneic HCT are at increased risk of breast cancer, especially after TBI-containing conditioning, and should undergo regular screening for breast cancer.

In a single-institution study from North America, four cases of papillary thyroid cancer occurred in 5001 patients who underwent auto- and allo-HCT, with a median follow-up of 7.4 years after HCT,[10] and the incidence of differentiated thyroid cancer was higher than that in the general population (SEER 2012 data: 14.9 cases of DTC per 100,000 individuals; the ratio of observed to expected cases was 5.36). The patient in our cohort had relapsed refractory CLL and underwent RIC allo-HCT from a matched sibling donor with 2 Gy TBI plus fludarabine conditioning and cyclosporine plus mycophenolate as GVHD prophylaxis. The patient was found to have second papillary thyroid cancer on routine follow-up without symptoms 33 months after HCT and remained disease free after total thyroidectomy and radio-iodine ablation for over 11 years.

Of our 126 survivors after autologous HCT, three patients had MDS/AML patients and one had bi-phenotypic ALL. The cumulative incidence was 5% at 10 years and 15% at 19 years. The median lag time between transplant and second MDS/AML occurrence was 108 months (range: 60–199 months). The first lymphoblastic lymphoma patient was diagnosed at the age of 18 years and underwent intensive induction polychemotherapy (according to the GMALL protocol), followed by high-dose BEAM and then autologous HCT. The second MDS/AML diagnosis was made 199 months later; however, the patient died of relapsed refractory AML even after allo-HCT from a matched unrelated donor. The second patient had relapsed follicular lymphoma with large cell transformation, and the second MDS occurred 65 months later. The MDS was classified as low risk, and she has been under observation without treatment for over 8 years as of this submission. The third and fourth patients were diagnosed with plasma cell myeloma without exposure to alkylating agents until autologous HCT was performed (BEAM conditioning). They were diagnosed with second AML (inv 3) and ALL (bi-phenotypic) 108 and 60 months later, respectively. They remained leukemia free for over 4 years after allogeneic HCT or intensive chemotherapy. However, they both had a relapse of myeloma during subsequent follow-up and received daratumumab-containing salvage treatment. They have since been in complete remission.

High-dose chemoradiotherapy with autologous stem cell rescue is known to increase the risk of therapy-related myelodysplasia or acute myeloid leukemia (t-MDS or t-AML). A single-institution study reported an estimated cumulative probability of developing morphologic t-MDS/AML of 8.6% ± 2.1% at 6 years.[11] In addition, multivariate analysis revealed that pretransplant radiation and primed with VP-16 for stem cell mobilization were associated with the most significantly increased risk.[11,12]

A retrospective multi-institutional study showed the impact of prior cytotoxic therapies on clinical outcomes.[13] Compared to patients with other second malignancies, therapy-related ALL (t-ALL) patients had a significantly shorter interval between the first malignancy and ALL diagnosis, and a higher frequency of poor-risk cytogenetic features, including KMT2A rearrangements and MDS-like abnormalities (e.g. monosomal karyotype, similar

to our patient who developed bi-phenotypic ALL). A variety of mutations were observed in the patients, with most of the patients exhibiting mutations more commonly associated with myeloid malignancies (e.g. DNMT3A, RUNX1, and ASXL1), whereas the others had ALL-type mutations (e.g. CDKN2A and IKZF1). Collectively, their results support that t-ALL is a distinct entity based on its biological and clinical features. As this is a high-risk category, allogeneic HCT should be considered.

The cumulative incidence of second malignancies after hematopoietic cell transplant should be considered. According to the annual reports provided by the National Ministry of Health and Welfare in Taiwan between 2012 and 2021, the annual incidence of cancer was between 96,695 and 121,979, with an age-standardized incidence between 296.7 and 315.9 for every 100,000 persons.[14] The latest data indicate that in 2021, 121,762 new cancer cases were diagnosed in Taiwan, translating to an age-standardized incidence rate of 330.8 per 100,000 men and 288.4 per 100,000 women. In our cohort, the cumulative incidence was 6% at 10 years and 16% at 19 years, nearly double the incidence at 10 years and triple that at 20 years compared with the general population. Therefore, screening for specific cancers, for example, skin, head and neck, breast, thyroid, and lung should be considered. Eliminating cancer-related risk factors, for example, smoking, alcoholism, and chemical exposure, is mandatory. sMDS/AML should be suspected if cytopenia occurs in these patients.

Acknowledgment

We thank our nursing practitioners and case managers: Yi-Mei Hsiao, Hwa-Mei Yen, Wan-Hwa Chow, Mei-Ling Kuo, Hitomi Yi-Wen Tsai, and Hsiao-Ping Chen; Epidemiology and biostatistics An-Cheng Feng and Yi-Hsuan Lin.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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