Chapter 31
Secondary Malignancies

Ashley Manning

Approximately 50,000 patients undergo hematopoietic stem cell transplantation (HSCT) worldwide each year. Advancements in the field have led to increased survival rates for these patients. Long-term HSCT survivors are at risk for developing secondary malignancies, representing the fourth leading cause of nonrelapse-related death in patients who survive more than 2–5 years after HSCT. Although relatively rare, secondary malignancies are often associated with significant morbidity and mortality. The incidence of secondary malignancies continues to increase across the survivor's lifespan requiring heightened awareness and ongoing surveillance for the duration of the transplant recipient's life.

31.1 General Risk Factors

1. Total body irradiation (TBI)
   a. Induces double-strand DNA breaks leading to genomic instability and molecular alterations
   b. Increased risk with higher total cumulative doses
   c. Decreased risk with fractionated dosing
2. Chemotherapy agents (see Table 31.1)
   a. Alkylating agents
      i. Latency period of 3–8 years.
      ii. Commonly associated cytogenetic abnormalities include 5-, 7-, 5q-, and 7q-.
      iii. May present with myelodysplasia.

A. Manning (✉)
Center for Hematologic Malignancies, Adult Blood and Marrow Stem Cell Transplant Program, Knight Cancer Institute, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, UHN 73C, Portland, OR 97239, USA
e-mail: manninas@ohsu.edu

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Table 31.1 Characteristics of tAML/MDS

	Alkylating agents	Topoisomerase II inhibitors
Latency	3–8 years	2–3 years
Incidence	2–20%	2–12%
Myelodysplastic phase	Present	Absent
FAB type	M1, M2	M4, M5
Cytogenetics	5-, 7-, 5q-, 7q-	11q23 deletion and translocation
Pathogenesis	Tumor suppressor genes, RAS mutations	Translocations

b. Topoisomerase inhibitors

   i. Latency period of 2–3 years.
   ii. Commonly associated cytogenetic abnormalities include 11q23 deletion and translocation.
   iii. Does not typically present with myelodysplasia.

c. Lenalidomide maintenance therapy post-autologous HSCT for myeloma

   i. Increasing utilization given studies which have shown a benefit in both progression-free and overall survival.
   ii. Randomized trials have shown an increased numerical incidence of secondary primary malignancies of 8% in patients receiving lenalidomide maintenance compared to 3–4% of those patients not receiving maintenance therapy. This observation was not statistically significant.
   iii. Cause is likely multifactorial.
   iv. Additional long-term follow-up will be required for confirmation of these findings.
   v. In a recently published trial of approximately 2500 multiple myeloma patients who received lenalidomide as primary therapy, the cumulative incidence of second malignancies at 5 years was 6.9%, compared to 4.8% in patients who did not receive lenalidomide.

      - 3.8% incidence of solid malignancy
      - 3.1% incidence of hematologic malignancy
      - Significantly increased risk of secondary hematologic malignancy in patients who received lenalidomide + melphalan compared with patients who received melphalan alone (HR 4.86)

3. Chronic graft-versus-host disease (cGVHD) following allogeneic HSCT

   a. Genomic alterations have been identified, especially in the epithelium of the oral cavity.
   b. Frequency of these events exceeds the incidence of secondary malignancies suggesting additional factors play a role in the pathogenesis.

      i. Complex immune defect associated with cGVHD

4. Oncogenic viruses including human papilloma virus (HPV) and Epstein Barr virus (EBV)
5. Predisposition to carcinogenesis
    a. Age
    b. Gender
    c. Lifestyle choices

31.2 Incidence

1. Reported cumulative incidence of secondary malignancies remains low
    a. Post-allogeneic HSCT
        i. 1.2–1.6 % at 5 years
        ii. 2.2–6.1 % at 10 years
        iii. 3.8–14.9 % at 15 years
    b. Post-autologous HSCT for lymphoma
        i. 2.54 % at 5 years
        ii. 6.79 % at 10 years
        iii. 9.14 % at 15 years
    c. Post-autologous HSCT for myeloma
        i. 5.3 % at 5 years
        ii. 11.2 % at 10 years

31.3 Onset

1. Typically, there is a latency period of 3–5 years preceding the development of secondary malignancies following HSCT but cases occurring earlier have been reported.

31.4 Types of Secondary Malignancies

1. Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) following **autologous** HSCT

a. Estimates of incidence of *therapy-related* MDS and AML (tMDS/AML) vary widely between 1 and 14 % at 3–15 years after autologous HSCT for lymphoma

   i. 3.1 % at 5 years
   ii. 4.5 % at 10 years
   iii. 6.8 % at 15 years

b. tMDS/AML is felt to be a consequence of the initial cytotoxic therapy for the primary malignancy rather than of the HSCT procedure and may represent a mutated stem cell pool that is transferred within the thawed cryopreserved product.

c. Risk factors

   i. Age
   ii. Extent of pre-HSCT therapy
   iii. Exposure to alkylating agents and TBI
   iv. Stresses imposed on stem cells during mobilization therapy and engraftment

      - Priming chemotherapy induces genotoxic damage in hematopoietic stem cells which are later infused during autologous HSCT
      - Proliferative stress during engraftment with many replication cycles has been proposed to contribute to genomic instability through telomere shortening

d. Prognosis

   i. Median overall survival of therapy related MDS/AML after autologous HSCT is 6–12 months although data regarding survival after salvage treatment with allogeneic HSCT are limited.

2. MDS and AML following **allogeneic** HSCT.

   a. Limited data are available regarding tMDS/AML following allogeneic HSCT, however case reports have been documented.

3. *Donor-derived* MDS/AML following allogeneic HSCT

   a. Incidence has been reported at < 1 %
   b. A European Group for Blood and Marrow Transplant (EBMT) study demonstrated median time to onset of 17 months with no specific risk factors identified

4. Posttransplant lymphoproliferative disorder (PTLD)

   a. A heterogeneous group of abnormal B-lymphoid proliferations that typically occurs in the setting of profound immunosuppression after allogeneic HSCT and presents as clinically aggressive and frequently fatal lymphomas

b. Vast majority are associated with EBV

   i. After allogeneic HSCT, PTLD is identified in the marrow derived, or adoptively transferred donor cells, differing from PTLD occurring in solid organ transplantation where it is of recipient origin

c. Incidence

   i. Cumulative incidence is 1–2% but may be as high as 8–10% among patients with multiple risk factors.
   ii. PTLD is rare following autologous HSCT and most commonly occurs in those patients requiring immunosuppressive therapy (i.e., steroids). However, there has been an increase in reported cases with use of CD34+ selected autologous HSCT in both adult and pediatric patients.

      − 80% of PTLD occur within 6 months to 1 year post-HSCT and incidence declines among survivors > 1 year post-HSCT.

d. Frequently presents with fever, lymphadenopathy, and hepatopslenomegaly
e. The two strongest risk factors are exposure to EBV and degree of immunosuppression, particularly T cell depleted allografts. Active surveillance, often weekly, for EBV reactivation using quantitative PCR is being increasingly advocated in high-risk patients.

   i. In vivo T cell depletion with antithimocyteglobulin (ATG) or alemtuzumab
   ii. Ex vivo T cell depletion
   iii. Alternative donor transplants such as haploidentical donors or cord blood

f. Preemptive therapy with CD20-active agents such as rituximab is being studied
g. Treatment requires restoration of immune response against EBV and elimination of EBV and neoplastic B cells.

   i. Withdrawal of immunosuppression if possible
   ii. Infusion of nonspecific donor T cells although the risk of GVHD is high
   iii. Infusion of EBV-specific T cells is under investigation

5. Secondary solid malignancies
   a. Skin/oral

      i. Occur in both autologous and allogeneic HSCT recipients
      ii. A large cohort of patients studied at The Fred Hutchinson Cancer Research Center (FHCRC) found the incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) to be 6.5% and 3.4% at 20 years, respectively, after allogeneic HSCT.
      iii. Total body irradiation (TBI) was a significant risk factor for BCC with higher incidence in younger and light-skinned patients.

iv. Acute GVHD increased risk of SCC whereas chronic GVHD increased the risk of both BCC and SCC.
v. Squamous cell carcinoma of the head and neck can arise from the buccal mucosa, salivary glands, gingiva, lip or tongue.
vi. Risk factors for oral cancer include oral cGVHD and underlying Fanconi anemia.

b. Lung

i. Recent study of patients receiving busulfan-cyclophosphamide conditioning reported an increased risk of lung cancer, especially among those with a prior history of smoking.

c. Hepatic

i. Long-term survivors with chronic Hepatitis C (HCV) represent a particularly high-risk cohort for cirrhosis and subsequent hepatocellular carcinoma.
ii. Incidence

- One historical retrospective analysis of patients infected with HCV during the HSCT period showed the incidence of cirrhosis to be 11 and 24% at 15 and 20 years, respectively
- Incidence of secondary cancer has been shown to reach 16% in HCV positive patients at 20 years.

d. Thyroid

i. Large cohort studied by the EBMT showed an increased incidence of thyroid cancer in patients who had undergone HSCT.

- The standardized incidence ratio of thyroid cancers in the population who underwent HSCT was 3.26 in comparison with the general population.

ii. Risk factors

- Younger age (<20) at HSCT was the strongest risk factor.
- Irradiation
- Female sex
- Chronic GVHD

e. Breast cancer

i. A retrospective analysis of 3337 female allogeneic HSCT survivors >5 years post-HSCT (FHCRC and EMBT registries) showed the cumulative incidence of breast cancer to be 11% at 25 years. This is compared to the overall incidence of 12% over a woman's lifespan.
ii. Risk factors

- Exposure of the breast tissue to radiation
- Disruption of ovarian function by alkylating agents
- Younger age (<18) at transplant

Table 31.2 Guidelines for screening for secondary solid cancers in allogeneic HSCT recipients

Site	Screening recommendations
Breast	Mammogram annually starting at age 40 years; begin at age 25 years or 8 years after radiation, whichever occurs later, in women who have received >20 Gy to chest region
Cervix	Papanicolaou (PAP) smear every year (for regular PAP test) or every 2 years (for liquid based PAP test); after age 30, if patient has had three consecutive normal tests, may screen every 2–3 years
Colorectal	Beginning at age 50, fecal occult blood annually and or flexible sigmoidoscopy every 5 years, or double-contrast barium enema every 5 years, or colonoscopy every 10 years; certain high-risk groups (i.e., patients with inflammatory bowel disease) may need earlier and more frequent screening
Lung	Yearly pulmonary examination with imaging as appropriate
Oral	Yearly oral cavity examination
Thyroid	Yearly thyroid examination
Skin	Skin examination as part of annual periodic health examination

HSCT hematopoietic stem cell transplantation

31.5 Screening and Preventive Practices

1. All HSCT recipients should be advised to reduce UV skin exposure through the use of high SPF sunscreen and/or skin coverage.
2. Patients should be advised of the risks of secondary malignancies and encouraged to perform screening self-examination such as breast, testicular, and skin.
3. Avoidance of high-risk behaviors is recommended including tobacco use, exposure to passive tobacco, or excessive unprotected UV skin exposure.
4. History and physical examination should be performed yearly, including symptom review for secondary malignancies in all HSCT recipients and the guidelines for screening for secondary solid cancers in allogeneic HSCT recipients should be followed (see Table 31.2).
5. Particular attention should be given to the oral cavity examination in patients with history of severe oropharyngeal chronic GVHD.
6. HPV vaccination is currently considered optional post-HSCT. Follow recommendations for general population in each country.
   a. Per CDC guidelines, HPV vaccination is routinely recommended for all 11- and 12-year-old girls and boys.
   b. The vaccine series can be started beginning at age 9.
   c. Vaccination is also recommended for 13- through 26-year-old females and 13- through 21-year-old males who have not completed the vaccination series.
   d. No data exist regarding the time after HSCT when vaccination can be expected to induce an immune response.

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