Secondary Neoplasia (Other than PTLPS)

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47.1 Definitions

Secondary neoplasia (SN) after HSCT includes any malignant disorder occurring after HSCT, irrespectively, if related or not to transplantation. For an individual patient, a clear relationship between HSCT and SN often cannot be provided. In this chapter, post transplant lymphoproliferative disorders are not discussed (see Chap. 45).

47.2 Types of Secondary Neoplasia After HSCT

	Therapy-related myeloid neoplasms (t-MN)[a]	Donor cell leukemia (DCL)[b]	Second solid neoplasms (SSN)[c]
Definition	t-MDS or t-AML after exposition chemo or radiation therapy	Hematologic neoplasms occurring in grafted donor cells	Solid cancers of any site and histology occurring after HSCT
Occurrence	Mainly after auto-HSCT Not excluded after allo-HSCT[d]	After allo-HSCT only	After allo-HSCT and auto-HSCT
Appearance	Within the first 10 years mainly	Variable	Increasing incidental rate with longer follow-up
Prognosis	Poor	Poor	Depends mainly on the cancer type

[a]Pedersen-Bjergaard et al. (2000); Engel et al. (2018)
[b]Sala-Torra et al. (2006); Wiseman (2011)
[c]Kolb et al. (1999); Rizzo et al. (2009)
[d]Yamasaki et al. (2017)

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47.3 Pathophysiology

47.3.1 Therapy-Related Myeloid Neoplasms

t-MN are mainly associated with cytotoxic chemotherapy and radiation therapy that the patient has received either before HSCT or as conditioning. The causal role of ionizing radiation in the development of myeloid neoplasms has been demonstrated in atomic bomb survivors of Hiroshima/Nagasaki and in medical radiation workers employed before 1950.

Responsible cytotoxic drugs:

- Alkylating agents, anthracyclines, and topoisomerase II inhibitors.
- To a lesser extent antimetabolites and purines analogs.
- Controversy exists on the role of azathioprine, methotrexate, hydroxyurea, and 6-mercaptopurines used for the treatment of malignant and nonmalignant diseases.

t-MN occur mainly after auto-HSCT, where the healthy HSC has been exposed to cytotoxic effect. Rarely t-MN can be observed after allo-HSCT, despite the donor cells have not been exposed to cytotoxic agents. Persistent microchimerism with few exposed residual recipient cells may explain the development of t-MN after allo-HSCT. The incidence of t-MN after allo-HSCT might increase, since chimeric states are observed more frequently after RIC-HSCT.

Today, increasingly cytotoxic drugs are applied after the allo-HSCT, either as GVHD prophylaxis (post transplant CY) or to prevent disease recurrence (post transplant maintenance). We do not yet know whether these procedures are at risk for t-MN after allo-HSCT.

47.3.2 Donor Cell Leukemia

The cause of donor-derived hematological malignancies remains speculative. Two different mechanisms may be involved (Sala-Torra et al. 2006; Wiseman 2011):

- Malignant clone transmitted from the donor to the recipient
- Malignant transformation in the recipient

Malignant clones transferred to the recipient are mainly of lymphoid origin, observed in older donors, and may evolve into a lymphoid neoplasm in the immunosuppressed host. Myeloid clone transfer has not been reported. However, systematic NGS analysis might allow to detect myeloid clones transmitted to the recipient.

Malignant transformation in the donor cells is probably of multifactorial causes:

- Premature aging of the donor hematopoiesis in the recipient, more inclined to develop a leukemia
- Abnormal microenvironment
- Genetic predisposition
- Acquired environmental factors

47.3.3 Second Solid Neoplasms (SSN)

Little is known about pathogenesis of SSN after HSCT. An interaction between cytotoxic treatment, genetic predisposition, environmental factors, viral infections, GVHD, and its immunosuppression may play a role.

Two main types of SSN (Rizzo et al. 2009):

- Radiation-related SSN
  - Proven for thyroid, breast, and brain cancers
  - Occur after a long latency (≥10 years after radiation)
  - Is dose related
- GVHD/immunosuppression-related SSN
  - Squamous cell carcinoma of the skin and oropharyngeal area
  - Short latency
  - Can occur at different localizations

Association with viral infection

- HCV infection associated with hepatocellular cancer
- HPV associated with cervix cancer

47.4 Frequency and Risk Factors (See Table 47.1)

47.4.1 Remarks on SSN

The CI of second solid cancer is 2.2% at 10 years and 6.7% at 15 years (Rizzo et al. 2009).

Increased risk for SSN after HSCT has been demonstrated from breast, thyroid, skin, liver, lung, oral cavity and pharynx, bone and connective tissues cancers and malignant melanoma.

An individual patient can present several subsequent different SSN after HSCT. Up to five different solid cancers have been observed in a patient treated with allo-HSCT.

Table 47.1 Frequency and risk factors

Type of SN	Frequency	Risk factors
t-MN	Great variability on the CI of t-MN after auto-HSCT • In lymphoma patients between 1% at 2 years up to 24% at 43 months • Lower CI for patients treated for breast cancer, germ cell tumor, and multiple myeloma • Rare n-MN after HSCT for AID CI depends mainly on pretransplant cytotoxic therapy and the use of TBI CI of t-MN after allo-HSCT: 0.06-0.67% at 3 years[a]	• Quantity of pretransplant chemotherapy (see pathogenesis) and local radiotherapy • Conditioning with TBI • Older age at HSCT t-MN are mainly observed after HSCT for lymphoma (NHL, HL)
DCL	Rare complication, with a CI <1% at 15 years Possibly underestimated (difficulty to prove donor type of malignant cells) Could represent up to 5% of post transplant leukemia "relapses"	No clear risk factor defined (too few, heterogeneous DCL) Possible risk factors[b] • Malignant donor clone in the transplant • G-CSF therapy • In vivo T cell depletion • Multiple transplantations
SSN		
Breast, thyroid, bone, melanoma, connective tissue, brain, BCC	Breast cancer: 11% at 25 years[c] Thyroid cancer: SIR 3.2 compared to general population[d] BCC: 6.5% at 20 years[e]	Radiation before HSCT or TBI Younger age at radiation Longer follow-up Light-skinned patients (BCC)
SSC of skin, oral cavity, and esophagus	SCC of the skin: 3.4 at 20 years[f]	Chronic GVHD Prolonged GvHD therapy IS including azathioprine Male sex Unrelated with radiation At any time after HSCT
Hepatocellular carcinoma	Patients with HCV infection: CI 16% at 20 years[g]	HCV infection Cirrhosis
Lung cancer	SIR 2.59 after BuCy[h]	Conditioning with Bu-Cy Smoking prior to HCT
Cervix cancer		HPV reactivation
Melanoma		T cell depletion

BCC basal cell carcinoma of the skin, *SSC* squamous cell carcinoma, *CI* cumulative incidence, *AID* autoimmune disorders, *SIR* standardized incidence ratio

[a]Yamasaki et al. (2017)
[b]Engel et al. (2018)
[c]Friedman et al. (2008)
[d]Cohen et al. (2007)
[e]Leisenring et al. (2006)
[f]Curtis et al. (2005)
[g]Peffault de Latour et al. (2004)
[h]Majhail et al. (2011)

Colorectal cancers have not been proven to be increased after HSCT. In non-transplanted cancer patients, second colorectal cancers are increased when treated with abdominal radiation (Henderson et al. 2012; Rapiti et al. 2008; van Eggermond et al. 2017).

So far there are few long-term data on SSN after RIC. A single-center study shows an increased rate of SSC compared to MAC during the first 10 years post-HSCT (Shimoni et al. 2013). There are not yet data on CI of SSN >10 years after RIC. SSN associated with TBI conditioning (breast, thyroid) might be lower after RIC than MAC.

47.5 Screening (Majhail et al. 2012) (See Also Chap. 21)

47.5.1 Therapy-Related Myeloid Neoplasms

Annual monitoring of full peripheral blood counts during the first 10 years after auto-HSCT (most t-MN occur within 10 years after HSCT)

In case of unexpected abnormalities (increased MCV, cytopenia, dysplasia in peripheral blood, monocytosis), extended analysis of blood and bone marrow (including cytogenetics and NGS)

47.5.2 Donor Cell Leukemia

Chimerism monitoring of the malignant cells in case of "relapse" or new hematological malignancy after allo-HSCT.

Whether search of an abnormal clone in the donor should be performed in case of donor origin of the malignancy remains controversial.

47.5.3 Second Solid Cancer (Socie and Rizzo 2012)

Lifelong screening for SSN is recommended after auto-HSCT and allo-HSCT.

General recommendations are:

- During annual control, clinical screening, reviewing for possible symptoms of SSN.
- Receive at least country-specific general population recommendations for cancer screening.
- Be informed and counseled about the risk of SSN.

Specific recommendations are included in Table 47.2.

Table 47.2 Screening for secondary solid cancer after HSCT

Skin	*All patients* Encouraged to • Perform regularly genital/testicular and skin self-examination • To avoid unprotected UV skin exposure Skin examination by dermatologist every 1–2 years *Patients at risk* More frequent examination by dermatologist • After first skin cancer • Patients with chronic skin GvHD
Oral cavity and pharynx	*All patients* Examination during annual control *Patients at risk* Annual control by specialist if severe oral and pharynx GvHD Histology in case of suspicious lesion
Thyroid	*All patients* Annual thyroid palpation to identify suspicious thyroid nodules *Patients at risk* (patients at risk after TBI or local radiation) Regular thyroid ultrasound Fine needle aspiration in case of a suspicious nodule

Breast	*All patients* Discuss breast self-examination with their physician *Patients at risk* Screening mammography every 1 to 2 years starts at the age of 25 or 8 years after radiation, whichever occurs later, but not later than age of 40 years
Cervix	*All patients* Screening with pap smears every 1–3 years in women older than 21 or within 3 years of initial sexual activity, whichever occurs earlier
Lung	*All patients* Encouraged to avoid smoking and passive tobacco exposure *Patients at risk* Patients at risk (high-dose busulfan conditioning and smoking), chest CT
Liver	*Patients at risk* Patients with known HCV infection should be assessed for fibrosis/cirrhosis of the liver 8–10 years after HSCT (biopsy; fibroscan)
Colorectal	*All patients* Screening should start at age 50 in absence of a family history (first-degree relative diagnosed with colorectal cancer before age 60): annual fecal occult blood testing, sigmoidoscopy every 5 years, with fecal occult testing every 3 years, or colonoscopy every 10 years
Prostate	*All patients* No specific recommendations

47.6 Treatment

Neoplasm	Treatment
t-MN	Same treatment than de novo myeloid neoplasms Early donor search and rapid allo-HSCT[a] Decision-making including consideration of cumulative toxicity due to previous HSCT
DCL	No standard treatment Treatment depends on the nature of disease Reported treatments[b] • Retransplantation • Conventional chemotherapy • DLI • Palliation
SSN	Should be treated as de novo cancers of the same type

[a]Finke et al. (2016); Kroger et al. (2011); Metafuni et al. (2018)
[b]Engel et al. (2018)

47.7 Outcome

Neoplasm	Outcome
t-MN	Generally very poor Median survival of 6 m Identical outcome than t-MN in general
DCL	Few data available In most cases, mortality high and OS poor In a small series of 47 DCL, median survival 32.8% months Death mainly due to progression or relapse of DCL
SSN	Mainly dependent on the type of SSN[a] Favorable outcome • Thyroid, breast, prostate, melanoma, cervix Intermediate outcome • Oropharyngeal, colorectal, bladder, renal, ovarian, endometrial Poor outcome • Pancreas, lung, brain, hepatobiliary, esophageal

[a]Ehrhardt et al. (2016); Tichelli et al. (2018)

Key Points

- Three types of secondary neoplasia may occur after HSCT: therapy-related myeloid neoplasms (t-MN), mainly after autoHSCT; donor cell leukemia (DCL) after allo-HSCT; second solid neoplasia (SSN) after auto-HSCT and allo-HSCT.
- Pretreatment or conditioning with radiation and/or chemotherapy including alkylating agents, anthracyclines, and topoisomerase II inhibitors is mainly responsible for t-MN.
- DCL are extremely rare and are either transmitted from the donor or newly transformed in the host.
- Non-squamous second solid cancers (breast, thyroid, brain, etc.) are strongly related to local radiation or TBI and occur with long delay after HSCT. Squamous cell carcinoma of the skin, the oral cavity, and the pharynx is related with chronic GVHD and can occur early after HSCT.
- Outcome of t-MN is poor, and allogeneic HSCT represents the only curative treatment.
- Outcome of SSN depends mainly on the type of second cancer; second solid cancer should be treated as a de novo cancer of the same type.

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