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REVIEW

# Optimal Delivery of Follow-Up Care After Allogeneic Hematopoietic Stem-Cell Transplant: Improving Patient Outcomes with a Multidisciplinary Approach

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**Abstract:** The increasing indications for allogeneic stem-cell transplant in patients with hematologic malignancies and non-malignant diseases combined with improved clinical outcomes have contributed to increase the number of long-term survivors. However, survivors are at increased risk of developing a unique set of complications and late effects, besides graft-versus-host disease and disease relapse. In this setting, the management capacity of a single health-care provider can easily be overwhelmed. Thus, to provide appropriate survivorship care, a multidisciplinary approach for the long-term follow-up is essential. This review aims at summarizing the most relevant information that a health-care provider should know to establish a follow-up care plan, in the light of individual exposures and risk factors, that includes all organ systems and considers the psychological burden of these patients.

**Keywords:** long-term, complications, allografting

## Introduction

Allogeneic hematopoietic stem-cell transplant (HSCT) has been used for more than 50 years to treat hematologic malignant and non-malignant diseases otherwise incurable. Over the decades, the number of patients undergoing allogeneic HSCT has gradually increased[1] given the expansion of indications for HSCT in older patients,[2] and the availability of alternative stem-cell sources such as cord blood[3] and haploidentical transplant.[4] Improved outcomes appear associated with the reduction of organ damage, infections, and severe acute graft-versus-host disease (aGvHD).[5] However, many issues for long-term survivors remain to be addressed. In this review, we will discuss the most important transplant-related late effects and stress the importance of a multidisciplinary approach to further improve clinical outcomes and quality of life (QoL) in transplant patients.

## Role of Long-Term Follow-Up After Allogeneic Hematopoietic Stem-Cell Transplant

Most deaths after HSCT occur within the first 2 years. The projection for long-term survival for 2-year survivors is, however, around 80–90%, though life expectancy remains lower than in general population.[6–8] A prospective observational study conducted on 1022 survivors, transplanted between 1974 and 1998, reported that 66% had at least one chronic condition and 18% had severe or life-threatening conditions, in particular those with active chronic GvHD (cGvHD), whereas rates were 39% and 8%

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in their healthy siblings, respectively (p< 0.001).[9] In another study, after a median follow-up of 7.1 years, HSCT survivors had experienced significantly more frequent hospitalizations (280 vs 173 episodes per 1000 person/years, p=0.001).[10,11]

Given the risks and potential consequences of late complications, there is a strong need for appropriate systematic long-term follow-up (LTFU) for transplant survivors to optimize clinical outcomes. Unfortunately, there are only a few clinical trials focused on screening and preventive practices among HSCT recipients. Most of the current recommendations and guidelines are not evidence-based and are supported by retrospective reports focused on single specific late complications or extrapolated from non-transplant cancer survivors. With the overall increased number of long-term transplant survivors, organized multidisciplinary LTFU programs remain an unmet clinical need.

## Psychological Impact of Follow-Up Care

HSCT represents a very stressful event that can compromise patient QoL even many years after it.[12–14] HSCT may have several severe psychological consequences that may be sometimes underestimated. Patients frequently report symptoms of distress, anxiety, depression, fatigue, post-traumatic stress disorder, psychosexual dysfunction, cognitive dysfunction, fear of malignancy recurrence, memory concern as well as poor QoL. Even though emotional distress does not always reach levels of clinical anxiety or depression, it can easily prevent good QoL.

Fatigue is one of the most persistent physical symptoms following transplant. Physical exercise serves as an effective intervention in reducing the severity of fatigue and improving QoL of cancer patients and survivors.[15,16] Females reported a greater prevalence of sexual dysfunction when compared with males, which, in turn, could worsen anxiety and depression. Infertility is also a common concern after transplant. Both health-care providers and patients are frequently reluctant to discuss sexual issues. The use of standardized questionnaires associated with the assessment of gonadal function could help to timely diagnose sexual dysfunctions and refer patients to specialists for further management.[17] However, most HSCT survivors can return to pre-transplant levels of QoL levels in about one year. Several studies reported that poorer pre-HSCT physical health, younger age, female gender, low educational level, low social support, physical symptoms, and cGvHD represent risk factors that can impair this recovery. Moreover, HSCT survivors may also have difficulties in social and working reintegration.[13,14,18-22]

General or transplant-specific questionnaires for multidimensional assessment of QoL can be used to assess the global well-being over time.[23,24] The Functional Assessment of Cancer Therapy and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire developed modules specific for cancer treatment and HSCT (FACT-BMT, EORTC QLQ-C30),[25,26] while the Short Form (36-item) Health Survey (SF-36) questionnaire[27] provides a general measure of QoL not specific for cancer, and is generally used in long-term survivors.

The transition from post-acute convalescence to LTFU is a complex and delicate process. Patients have to deal with a role change not only in health aspects but also in their daily life. For this reason, individualized survivorship care plans should include attention to the psychosocial needs of patients. During LTFU surveillance and screening, strategies should be activated not only for medical late-effects but also for early signs of psychological and emotional distress, which may increase during the transition process.[28–30]

Health-care providers should increase awareness in patients and their families about the potential late effects of cancer therapies. Since patient's attitude toward his illness and treatment is an important factor, survivors should be encouraged to be involved in their own long-term care.[29] Patients with lower levels of informational needs and fewer information barriers report better QoL and less anxiety and depression.[31] By contrast, survivors with low reported overall health are often related to poor coping and difficulty in adapting to disease, involving more unmet needs. Hence, survivorship care plans should be written in a non-medical and easy-to-understand language. Moreover, patient's own perception of illness and survivorship may impact on his levels of unmet needs. Clinician should take into consideration the patient's beliefs and expectations on his health.

Non-compliance or abandonment of LTFU may be due to several factors like patient's physical discomfort, misunderstanding, and uncertainty about the importance of regular evaluation, poor communication, and inadequate information from clinicians on diagnosis, treatments, and late-effects. Thus, it is very important to establish a good relationship between the patient, the relatives, and physicians. This relationship should be based on trust, good communication, dialogue, and mutual information, in order to improve adherence to follow-up care. However, many survivors may be scared that a regular check-up can lead to unveil new pathology that some of them would rather ignore.[29] Furthermore,

a long distance from the follow-up center increases risk for non-compliance.

Finally, it should be also considered that many patients and caregivers have been unable to work during HSCT treatments and during the following months, leading to less income and lack of economic stability.

In order to address survivors' concerns and improve their overall QoL, psychological and psychosocial interventions (eg, education, exercise, counseling, cognitive behavioral therapy, psychotherapy) should be provided for more vulnerable patients after HSCT, in the contest of a multidisciplinary LTFU care.

## Delayed Complications After Transplant

One of the main post-transplant long-term complications is represented by cGvHD, and its management remains challenging because of polymorphic manifestations and lack of valid biomarkers for the diagnosis and assessment of disease activity. However, management of cGvHD requires dedicated expertise, and many published consensus guidelines comprehensively address and provide recommendations.[32,33]

This review aims at post-transplant long-term patient care, besides GvHD and hematologic disease relapse, although consequences of GvHD and hematologic disease might impact on patient health status. Patients surviving after allogeneic HSCT might have a long and complicate medical history; thus, Figure 1 summarizes the most relevant information that a health-care provider should keep in mind to establish an LTFU care plan based on individual exposures and risk factors, whereas Figure 2 detailed our proposal to monitor potential complications by organ involvement.

### Cardiovascular and Metabolic Complications

Cardiovascular diseases (CVD) represent one of the most frequent causes of morbidity and mortality in HSCT recipients[34] and HSCT survivors have a fourfold higher risk of developing CVD compared with the general population.[35] Cardiovascular (CV) alterations can be directly induced by certain anticancer treatments. Pre-HSCT exposure to anthracyclines-based chemotherapy regimen and/or chest irradiation represents the better-described risk factors for the development of late (>1 year after HSCT) cardiotoxicity.[36,37] Anthracyclines, with a dose-dependent effect, can induce non-ischemic alterations in myocytes, through the generation of reactive oxygen species (ROS), leading to a dilated cardiomyopathy.[38] In patients with a previous exposure to anthracyclines, the use of potentially cardiotoxic treatments (eg, high-dose cyclophosphamide or TBI for conditioning) may further compromise the cardiac function. Younger and older patients at the time of administration, as well as females, seem to have the higher risk of anthracycline-induced cardiotoxicity.

As far as regards radiation exposure, it is well known that RT can impair all cardiac structures (myocytes, valves, pericardium, coronary arteries), via a common pathophysiological pathway dominated by a microvascular damage.[39] Also GvHD seems to be able to induce a chronic injury in vascular wall, determining an endothelial infiltration by cytotoxic T-lymphocytes.[40]

Beyond the direct CV damage induced by chemotherapy and/or RT, metabolic alterations have gained importance as determinant of CDV in cancer survivors in recent years,[41] even if the mechanisms at the basis of the increased incidence of metabolic syndrome (MS) in HSCT survivors are not completely understood.[34,42] According to Tichelli et al, 15 years after transplant survivors of allogeneic HSCT showed a 7.5% cumulative incidence of CV events (whereas a 2.3% incidence was found after autologous HSCT). Moreover, being affected by 2 out of 4 CV risk factors (hypertension, dyslipidemia, diabetes mellitus, and obesity) predicted the risk of these CV events.[43]

Obesity is a central component of MS. A negative correlation between pre-procedural obesity and the onset of post-transplant complications has been well established.[44] Moreover, transplanted patients are at increased risk of overweight and sarcopenic obesity (ie, a predominance of fat vs lean mass), independently from pre-HSCT weight, and in general populations, sarcopenic obesity represents a better predictor of CVD in comparison with the simple increase of the body mass index (BMI).[45,46] The corticosteroids administration, together with a prolonged physical inactivity, seems to be the main responsible for these alterations in body composition.[47,48]

In HSCT recipients, the prevalence of lipid profile alterations is higher than in general population. The Bone Marrow Transplant Survivor Study estimated a prevalence of 12.5%, 36.6%, and 45.0% (at baseline, after 1, and after 5 years, respectively) for subjects who underwent allogeneic HSCT.[49] A 2-fold risk of new-onset dyslipidemia has been demonstrated for survivors of allogenic HSCT when compared to patients who have received autologous transplant.[43] Moreover, hypercholesterolemia and/or hypertriglyceridemia were found in about 40% and 70% of these

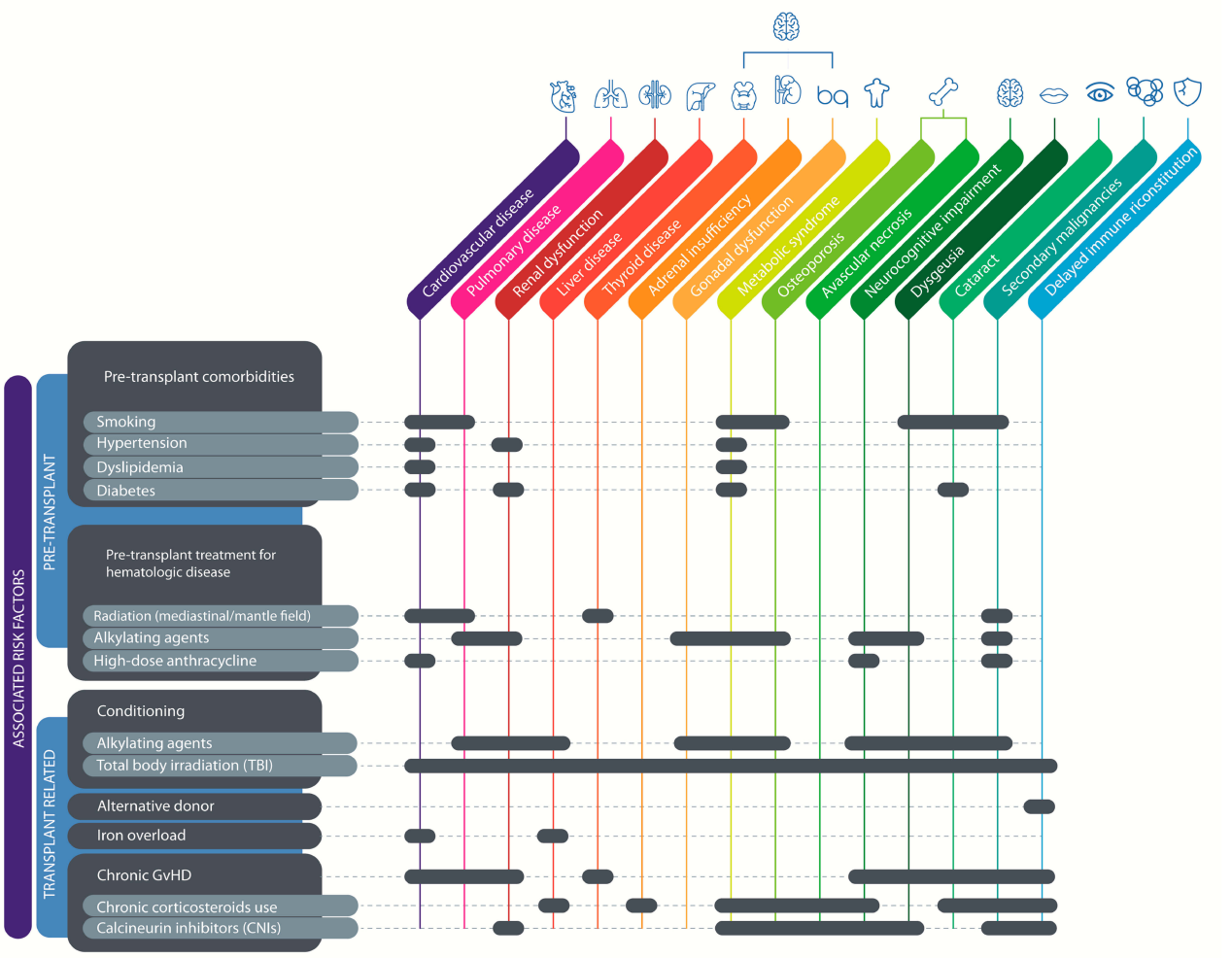


**Figure 1** Association between patient risk factors and long-term complications after allogeneic hematopoietic stem-cell transplantation (HSCT).

patients.[50,51] The main factors associated with high risk of dyslipidemia are family/personal history of hyperlipidemia, obesity, TBI, aGvHD and cGvHD, and chronic liver disease. Immunosuppressant drugs (eg, CNIs, corticosteroids, mTOR inhibitors) can induce hypercholesterolemia that may persist after withdrawal of these medications, but they can also influence the effect of statins.[52,53] The presence of hypogonadism and/or hypothyroidism, but also growth hormone deficiency (induced by anticancer treatments), can contribute to the alteration of lipid metabolism. Finally, renal insufficiency and nephrotic syndrome, which are observed in some cases after HSCT, can also lead to the onset of dyslipidemia or worsen a pre-existing lipid disorder.[54]

During HSCT or in the first period after the procedure, the use of corticosteroid and other immunosuppressive drugs can induce hyperglycemia that usually subsequently regresses.[55] In some patients, an alteration of glucose metabolism, ranging from insulin resistance to overt diabetes mellitus (DM), can longer persist or arise during the LTFU. Both in adult and pediatric patients, a DM incidence of 30% was reported within 2 years after allogeneic HSCT,[56] but a lower prevalence has been shown after a longer observation period.[34] When compared to sibling donors, patients transplanted during childhood showed a 3.6-folds risk of DM.[49] TBI exposure is the main risk factor for the development of DM after HSCT and a reduced pancreatic volume has been found in patients who received a radiation-based conditioning regimen, with a consequently impaired insulin reserve. After transplant, the risk of DM could be also increased by the presence of severe aGvHD and by administration of corticosteroids (mostly when cumulative prednisone equivalent dose is >0.25 mg/kg/day), as well as unfavorable dietary habits, lower physical activity, and family history of DM.[34]

HSCT survivors also show an increased risk of hypertension, when compared with the general population. Moreover, data from the Bone Marrow Transplant Survivors Study

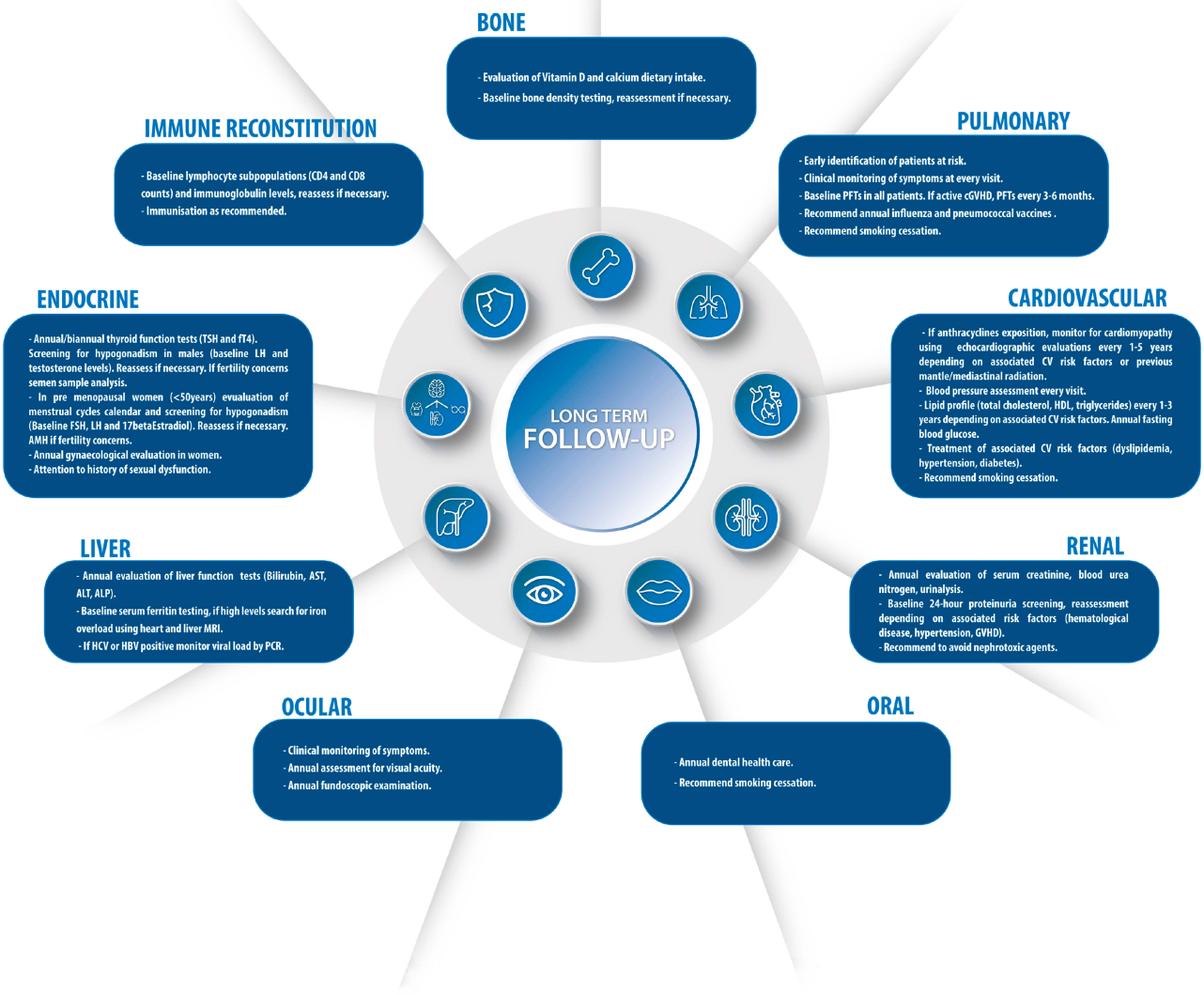


**Figure 2** Our proposal to monitor potential complications by organ involvement.
**Abbreviation:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMH, anti-müllerian hormone; AST, aspartate aminotransferase; CV, cardiovascular; FSH, follicle-stimulatiog hormone; ft4, thyroxine; HBV, Hepatitis B virus; HCV, Hepatits C virus; HDL, high-density lipoprotein; LH, luteinizing hormone; PCR, polymerase chain reaction; PFTs, pulmonary function tests; TSH, thyroid stimulating hormone.

showed that, after adjustment for age, sex, race, and BMI, patients who had received an allogeneic HSCT have a 2-fold risk of hypertension than sibling donors or autologous HSCT survivors.[49] CNIs and steroids, commonly used to counteract GvHD, exert a pro-hypertensive effect, but probably this effect ends after drug discontinuation.[56] Moreover, it has been reported that GvHD itself, inducing pro-inflammatory response and endothelial damage, can play a role in pathogenesis of hypertension in transplanted patients. Finally, some as pre-transplant anticancer treatments have been suspected as potential causes of hypertension. Nevertheless, no difference in the incidence of hypertension was found in two large studies considering survivors of allogeneic HSCT with or without GvHD.[47,57]

Several recommendations have been published about management of CV risk in cancer patients, with some point of discordance. Anyway, some recommendations can be made. At every follow-up visit, patients should be asked about dietary habits and smoking, and clinicians must promote healthy life-stiles. Clinical examination should include measurement of blood pressure, body weight, and waist circumference. Depending on the risk factors (dose of

anthracyclines, previous mediastinal irradiation, age), direct cardiac toxicity should be evaluated by periodical echocardiography, at interval ranging from 1 to 5 years.[58,59] Finally, all patients should be screened, on the bases of previous exposures (eg, growth hormone deficiency in patients exposed to TBI during childhood), for the risk of concomitant endocrine dysfunction with potential impact on CV risk.

As far as regards the screening for MS, despite the limitations due to the discrepancy between available recommendations, evaluating fasting blood glucose annually and lipid profile once every 2–3 years could be reasonable during LTFU. Lifestyle modifications represent a crucial issue for the treatment and prevention of MS in cancer survivors as well as in general population. The promotion of smoking cessation, healthy diet, and physical activity is an essential component of the survivorship care.[41,52,60] No prospective, randomized studies are currently available in the specific population of HSCT survivors evaluating the efficacy of drug commonly used for treatment of MS (eg, antihypertensive, statins). As a consequence, drug categories recommended in general population should be also used in this specific context, taking into consideration the presence of comorbidities.[61] Finally, it should be highlighted that algorithms currently used to predict CV risk in general population are not validated in HSCT survivors and probably they underestimate the risk in this specific population, especially in younger patients.[41,62] Therefore, probably more stringent parameters for deciding whether to treat or not MS in HSCT survivors may be reasonable.

## Airway and Pulmonary Disease

Delayed pulmonary complications significantly contribute to morbidity and mortality. Advances in antimicrobial prophylaxis and treatments have led to a relative increase in non-infectious complications. Bronchiolitis obliterans syndrome (BOS) and cryptogenic organizing pneumonia (COP) are the most common late-onset lung complications.[63] However, real incidence is difficult to assess given the lack of standardized diagnostic criteria and terminology. A retrospective study showed a strong association between BOS and cGvHD, and by the National Institutes of Health (NIH) consensus criteria, BOS is the only manifestation to diagnose pulmonary cGvHD.[64,65] BOS is characterized by obstructive airflow limitation, secondary to fibrous obliteration of the small airways.[64] Pulmonary function tests (PFTs) show reduced forced expiratory volume in 1 second (FEV1), reduction in FEV1/forced vital capacity (FVC) ratio, and unexplained irreversible decrease of FEV1 over 2 years. In the absence of other features of cGvHD, it should also be associated with air trapping either on expiratory chest computed tomography (CT) or on PFTs.[66] Presentation is usually insidious, though clinical features may include dry cough, dyspnea, and wheezing. Some patients, however, may be asymptomatic. PTFs are usually performed at the onset of symptoms when abnormalities may be already severe. Thus, PFTs every 3–6 months are recommended in patients with active pulmonary cGvHD. COP, previously termed "bronchiolitis obliterans organizing pneumonia" (BOOP), is associated with restrictive alterations, secondary to interstitial deposition of fibroblasts within bronchioles, alveolar ducts, and alveoli.[67] Restrictive lung disease is defined by PFTs reduction in FVC, total lung capacity (TLC), and diffusion lung capacity for carbon monoxide (DLCO). Presentation is acute and includes fever, non-productive cough, and dyspnea. Chest CT usually demonstrates diffuse, peripheral patchy consolidation, ground-glass opacities, or nodular lesions.[68] Bronchoscopy with bronchoalveolar lavage (BAL) is recommended to rule out respiratory infections and can be combined with transbronchial biopsies for histology study. Open lung biopsy is rarely performed because of its invasive nature. Therapy of BOS and COP is based primarily on prednisone, and it benefits from a multidisciplinary approach including a pneumologist consultant.[63,69,70]

Late interstitial lung disease has been also reported following TBI and chemotherapeutic agents, including busulfan and cyclophosphamide. Besides, previous exposure to drugs that cause pulmonary toxicity, such as bleomycin, methotrexate, carmustine, or mantle radiation to treat the underlying malignancy may magnify and are well-known risk factors for the development of late pulmonary fibrosis in patients receiving HSCT.[71,72] A careful identification of patients who may progress to interstitial fibrosis is crucial, as diagnosis may be delayed due to a non-specific and insidious presentation. Symptomatic patients present with cough, progressive dyspnea, and restrictive pattern on PFTs.

All these patterns, together with a non-complete immunocompetence, led to an increase of infective complications involving bronchi and lung. Thus, inactivated vaccines and avoiding tobacco smoking are strongly advised.

A close cooperation between LTFU physician and a pneumologist consultant is strongly recommended to decide individually tailored diagnostic strategy and treatment of a transplanted patients with suspected lung complications. In this setting, in order to improve patients' outcomes, the careful monitoring of PFTs allows early

detection of lung complications and permits timely diagnosis and treatment.

## Endocrine Dysfunctions

### Thyroid

Thyroid gland abnormalities after HSCT include hypothyroidism, hyperthyroidism, and thyroid cancer. Radiotherapy (RT) is the main risk factor for hypothyroidism and thyroid cancer in transplanted patients. TBI represents the most common risk factor, but pre-HSCT head/neck or upper thorax RT should also be taken into account (eg, patients treated for lymphomas).

As it regards hypothyroidism, in transplanted patients it is almost always primary hypothyroidism. Indeed, cranial RT doses higher than those used for TBI are needed to damage the pituitary TSH-producing cells.[73] Moreover, since the probability of developing an underactive thyroid after RT is directly related to the radiation dose, hypothyroidism after TBI may be subclinical and not requires treatment.[74,75] The patients age at irradiation also impacts on the risk of hypothyroidism, which is lower in patients irradiated at age older than 10 years.[76] The effects of chemotherapy on thyroid function are less characterized. Anyway, in children, busulfan seems to enhance the detrimental effects of RT on thyroid function, causing hypothyroidism by itself.[77]

Instead, hyperthyroidism after allogeneic HSCT is rare and presumably it is mediated by the transfer of immunocompetent donor lymphocytes to the recipient by HSCT.[78]

Thyroid dysfunctions usually occur during the first years after transplant, but new cases have been reported more than 20 years after HSCT.[76] Hence, annual/biannual evaluation of thyroid function should be performed in patients at risk for hypothyroidism.

As it regards the risk of thyroid cancer, it is closely related to neck irradiation, while the role of chemotherapy is probably negligible. In irradiated patients, thyroid cancers are almost always well-differentiated tumors with papillary histology.[79] The dose–response relationship between thyroid irradiation doses and cancer risk is not linear: indeed, the relative risk increases linearly up to 15–20 Gy, where it peaks at about 15-fold, then it drops.[80] The risk of thyroid cancer, that persists for several decades after HSCT, is higher in females and in patients treated at a younger age. A peak of about 28-fold risk has been reported in patients who received RT before 5 years of age.[80]

Optimal surveillance strategy to screen for thyroid cancer patients at risk is still debated. Periodical neck ultrasonography (US) for early detection of thyroid nodules has been associated with optimal specificity and sensitivity, but also with false-positive results and unnecessary invasive procedures. On the other hand, the only neck palpation is characterized by a lower risk of unnecessary invasive procedures but burdened by a potentially higher risk of morbidity and mortality for thyroid cancer diagnosed at more advanced stages. According to the patient's preferences, US or neck palpation should be used as screening modality, also taking into account the experience of health-care providers. If US is chosen, it may be reasonable to perform the first examination 5 years after RT and, if normal, to repeat it every 3–5 years. No recommendation can be made for how long surveillance should be continued.[79,81,82]

### Adrenal Glands

Adrenal insufficiency was reported to occur in about 13% of patient after allogeneic HSCT and about 1% of patients after autologous HSCT. The main risk factor for adrenal insufficiency is the prolonged use of glucocorticoids, causing inhibition of hypothalamus secretion of corticotropin-releasing hormone (CRH) and pituitary secretion of adrenocorticotropic hormone (ACTH). Once steroid therapy is withdrawn, usually the hypothalamus-pituitary-adrenal axis spontaneously restores, unless the corticosteroid treatment is prolonged over a long time and involves high doses. Due to the relative resistance of pituitary ACTH-producing cells to radiation-induced damage, in patients who had received TBI alone the risk of central hypoadrenalism is minimal.[83] Anyway, some studies had reported late-onset ACTH-deficiency in patients submitted to TBI, generally together with deficiency of other pituitary hormones.[63,84]

Symptoms of adrenal insufficiency in this set of patients can mimic GvHD. Therefore, evaluating serum cortisol and serum ACTH at 8:00 a.m. is suggested in all patients who had received corticosteroids for a period >3 months at prednisone equivalent dose >7.5 mg/day. In case of not conclusive baseline test results, ACTH stimulation test should be performed. When adrenal insufficiency is confirmed, synthetic corticosteroids should be replaced with hydrocortisone 20 mg/day. In the case of adrenal insufficiency in patients without a previous history of steroid administration, higher starting dose of hydrocortisone is required (20 mg twice a day).[85]

### Gonadal Function and Fertility

Gonadal dysfunction is the most frequently observed late effect after HSCT. The gonads serve two functions:

hormone secretion and germ cells production. Even if the endocrine effects of gonadal damage are more relevant in clinical terms, infertility is a major psychological concern for both males and females after anticancer treatments.[86,87]

The potential risk of hypogonadotropic hypogonadism after radiation therapy involving the hypothalamic-pituitary region is well known. Anyway, gonadotropic cells are quite resistant to radiation-induced damage; thus, the dose given by the TBI is almost certainly unable to induce hypogonadotropic hypogonadism.[83]

As it regards primary gonadal insufficiency, both the testis[88] and the ovary[89] are highly sensitive to the toxic effects of radiotherapy and some chemotherapy agents (mainly alkylants).

In females, due to the close association between germ cells and endocrine cells of the ovary, the loss of fertility is always associated with the loss of hormonal production. Chemotherapy (mainly alkylating agents) and RT decrease the ovarian reserve, thus predisposing female patients to premature ovarian failure (POF). Anyway, until the occurrence of hypergonadotropic hypogonadism females may have normal ovarian function (ie, they are fertile and show normal hormone levels). The extent of ovarian damage is dependent on the radiation dose received by the ovaries[90] and the cumulative dose of chemotherapy drugs.[91] Patient's age at the time of treatment also influences the risk of hypogonadism, since the number of primordial follicles present at the time of treatment will determine the "fertility window", with progressively smaller doses required to produce ovarian failure with increasing age.[92]

In males the endocrine and reproductive functions are more separated – anatomically as well as functionally – than in females. The interstitial compartment of the testis, containing Leydig cells that produce and secrete testosterone, is much more resistant than seminiferous tubules to the damage induced by RT[93] and/or chemotherapy.[94] As a consequence, after anticancer treatments, patients often show impairment in fertility (ranging from oligospermia to azoospermia) but usually have a normal testosterone production.[94] Among chemotherapy, alkylating agents demonstrated the more detrimental effect on seminiferous tubules. Azoospermia may be transient or permanent, depending on whether anticancer therapies harm only differentiating germ cells or even the spermatogonial stem cells.[95]

In pre-menopausal women (<50 years), menstrual cycle calendar should be evaluated at every follow-up visit. Moreover, a baseline evaluation of FSH, LH, and 17β-estradiol should be performed at the entry in LTFU program and subsequently repeated if amenorrhea or significant alterations in menstrual cycles persist for at least 6 months. Anti-Müllerian hormone (AMH) levels should be assessed in women interested to explore their fertility potential. Hormone replacement therapy is recommended in the case of POF.[96]

In males, symptoms of sexual dysfunction should be investigated at every follow-up visit. Total testosterone and LH levels should be evaluated in all male HSCT survivors starting LTFU program. In patients who are interested to explore their potential fertility, semen sample analysis should be performed, preferably 2 years after the end of anticancer treatments, to avoid false positive, due to transient sperm impairment.[97,98]

## Ocular Complications

Almost 15% of patients who have undergone allogeneic HSCT develops major ocular complications, and cGvHD is the most frequent one.[99] New onset of dry painful eyes, cicatricial conjunctivitis, keratoconjunctivitis sicca, punctate keratopathy, and blepharitis are the most common clinical manifestations of ocular cGvHD.[100] Conjunctiva can be subjected to cicatricial changes, and forniceal conjunctival symblepharon with consequent lid scarring represents the most dangerous complication of superior limbic keratoconjunctivitis.[101] Another possible evolution of severe ocular GvHD is punctate keratopathy, characterized by corneal filament with subsequent corneal erosion, ulcerations, and perforations and severe infections.[101] In order to prevent blindness, ocular GvHD should be recognized and referred to a specialist for prompt and adequate treatment. Prophylactic measures of photoprotection and artificial tears to maintain a humified environment should be advised.

Chronic use of corticosteroids and other immunosuppressive therapy (IST) can lead also to early cataract formation, increase of intraocular pressure with development of glaucoma, ischemic microvascular retinopathy, hemorrhage, optic disk edema, and infectious retinitis (especially CMV-related).[30]

Furthermore, it is well known that cranial irradiation and TBI-based conditioning regimens are cataractogenic.[102,103] According to data, the cumulative incidence of cataracts ranges from 36% in children at 15 years,[104] to 50% in adult at 10 years after allogeneic HSCT.[105] Besides, dose fractionation seems to play an important role. Indeed, it can amount

up to 60% in patients receiving single-dose TBI, 43% if six or less fractions were administered, and 7% if total radiation dose was fractionated in more than six fractions.

As screening recommendations for long-term survivors, a periodic assessment for visual acuity with eventual fundoscopic examination should be performed, taking care of surveillance for cataract formation, increased intraocular pressure and infective signs, performing microbiological culture whenever needed.[106]

## Oral Complications and Dental Abnormalities

Comprehensive oral supportive care should be an integral component of allogeneic HSCT patient management, and a multidisciplinary team approach may reduce the risk for medical complication and health-care resource utilization, improving patient suffering and long-term outcome.

Oral cavity is one of the main and sometimes the only site of cGvHD involvement.[107] Extensive oral cGvHD can cause severe pain and disability, but also permanent reduction and alteration in saliva production.[108] Xerostomia, oral hypersensitivity, and burning can lead to oral discomfort to normally tolerated agents like spices and increase infective risk because of retrograde spread of colonizing microflora up ductal structures. Consequently, quickening of dental decay and caries, and hindering of enamel and dentine remineralizing due to calcium and phosphates salivary reduction, may significantly impact on patient QoL. Topical management of oral cGvHD includes application of steroids (rinses, creams, or gels) and immunosuppressive agents. Oral hygiene protocols including brushing and flossing can prevent infection due to dental/periodontal disease. Fluoride therapy should be considered as remineralizing dental treatment. Mucosal lubrification by frequent sipping of fluids or artificial saliva, and sialagogue agents (like pilocarpine) improving salivary flow rates,[109] can increase oral moisturization. Of note, lichen planus-like hyperkeratotic white lines and plaques, associated with generalized mucosal atrophy, can be related to cGvHD but also worsened by prolonged chronic corticosteroid use.[110]

Besides, TBI may increase radiation damage to tissue overlying the metal surfaces of orthodontic fixed appliances, producing radiation backscatter.[111] Also, pre-existing oral/dental disease could contribute to oral complications after allogeneic HSCT; hence, pre-transplant oral evaluation remains mandatory.

Since oral infections, including gingivitis, periodontitis, and dental abscesses, can worsen oral cGvHD, patients should be encouraged to maintain an adequate oral hygiene.

Neurosensory toxicity related to chemoradiotherapy, calcineurin inhibitors (CNIs), and cGvHD can lead to taste dysfunction.[112]

Chemotherapy and especially TBI-based regimens can cause abnormalities in developing dental and/or craniofacial skeletal structures in children who undergo allogeneic HSCT,[113] including tooth buds damage, enamel hypoplasia, root-growth alterations, or complete agenesis. Besides, the younger age of patients, the higher risk of extent of dental abnormalities.[114]

Patients may have up to 30-fold risk increase for oral cancers 10 years after transplant.[115] The most common types are squamous cell carcinomas (SCC) and salivary gland tumors.[113,116] Concomitant cGvHD represents a risk factor for SCC,[117] and HPV infection[118] may also promote carcinogenesis.

Routine dental treatment including dental restorations should be resumed according to the immune reconstitution. Complete oral soft tissue and head/neck examination should be periodically performed during follow-up of all post-transplant survivors, to detect early potential head and neck dysplastic lesions. Patients should also be instructed to monitor oral lesions changes properly. For lesions not healing within 2–3 weeks, biopsy remains the only tool to discriminate malignancies.[30]

## Renal Dysfunction

Chronic kidney disease (CKD) is described in about 20–60% of patients.[119–122] Al-Hazzouri et al reported older age, hypertension, poor pre-transplant kidney function, diagnosis of multiple myeloma (MM), and use of CNIs for GvHD as risk factors for CKD.[123] Other authors reported that fludarabine administration was significantly associated with chronic renal impairment.[124]

CKD can represent the sequelae of an acute kidney injury, mostly related to viral nephropathy (BK virus)[125] or to CNIs-induced thrombotic microangiopathy.[126,127] Nephrotic syndrome develops in 6–8% of post-transplant patients,[128,129] as membranous nephropathy (MN) or minimal change disease (MCD). MCD is T-cell mediated, associated with earlier onset and better prognosis[130] while MN is due to immune-complexes recognizing podocyte antigens with auto- or alloantibodies.[131] First-line therapy with prednisone 1 mg/kg/day plus CNIs leads to a complete remission (CR) only in 27%

of patients.[130] Rituximab and/or mycophenolate mofetil (MMF) are used in refractory cases.[132] The majority of CKD remain, however, idiopathic. Inflammatory conditions may be involved in the pathogenesis, including GvHD and its nephrotoxic accompanying treatment,[122,133] but also previous extensive use of nephrotoxic antibiotics might play a role.[134] TBI-associated risk remains controversial.[122,134-136]

## Gastrointestinal Complications, Liver Impairment, and Iron Overload

Incidence and severity of gastrointestinal (GI) and liver complications after allogeneic HSCT have gradually declined over the past decade likely due to better strategies in preventing their onset such as more effective infectious prophylaxis and patient-tailored conditioning regimens.

GI manifestations of cGvHD include anorexia, nausea, vomiting, diarrhea, weight loss, failure to thrive, and wasting syndrome. However, drug toxicity, motility disorders, and infections may mimic the same symptoms.[66] Prolonged use of CNIs and cGvHD may also be associated with pancreatic atrophy and exocrine insufficiency leading to malabsorption that often improves with oral pancreatic enzyme supplementation.[137] Finally, prolonged GvHD, active over decades, can cause chronic GI inflammation with aspecific symptoms consisting of mild diarrhea and abdominal pain, sometimes secondary to intestinal pseudo-obstruction related to fibrotic cGvHD damage.[138]

Late liver toxicity can present both as acute hepatitis with protracted jaundice or as slowly progressive cholestatic disorder. Both presentations can be related to cGvHD. However, several medications (ie, CNIs and antimicrobial drugs) are associated with late drug-induced liver injury (DILI), usually leading to a reversible hepatic dysfunction after their interruption.[139] Reactivation of HBV and HCV leading to late liver abnormalities should always be ruled out. In fact, following the withdrawal of cytotoxic or immunosuppressive agents and the restoration of the immune function, T-cell immune-mediated destruction of the viral-infected hepatocytes might occur.[140–143] Thus, liver function tests and HBV-DNA and/or HCV-RNA should be monitored in the follow-up of all HBV or HCV carriers. During cGvHD treatment, the cumulative risk for HBV reactivation, even if only isolated anti-HBc antibodies are present, can involve up to 35% of patients, especially those previously treated with anti-CD20 antibodies, though prophylaxis with lamivudine deeply decreases the risk.[141,143,144] In the majority of cases, HCV hepatitis reactivation results in a chronic disease, being the cumulative incidence of cirrhosis progression about 11% at 15 years, and up to 24% at 20 years.[140,142]

Among other late liver complications, nodular regenerative hyperplasia and focal nodular hyperplasia are the most frequent ones, being usually asymptomatic unless portal hypertension due to sinusoidal injury develops.[145] As regards sinusoidal liver injury, prophylaxis with ursodiol should be used to mitigate cholestatic damage.[139,145]

Iron overload is a common late effect after allogeneic HSCT, reported in 30–60% of long-term survivors.[120,146] Iron accumulation is a consequence of chronic transfusion dependence, both in pre- and post-transplant period. The excess iron can interfere with the delicate intracellular iron balance, thus generating damaging reactive oxygen species (ROS).[147] Iron overload diagnosis should be made monitoring serum ferritin levels and measuring tissue iron concentration by magnetic resonance imaging (MRI) and/or liver biopsy. The most direct and accurate exam to determine liver iron concentration (LIC) is liver biopsy,[106] but potential serious complications related to this invasive procedure led to an increased use of indirect tests, such as MRI and FerriScan.[148] Since ferritin can be elevated in other settings such as hepatic and systemic inflammation, additional tests to rule out inflammatory conditions, MS, and alcoholism are required. Hence, transferrin saturation could be preferred. However, liver tests are often normal among patients, with the exception of increased GGT levels.[145] The persistence of high LIC can exert long-term risk contributing to morbidity after allogeneic HSCT.[149] Iron overload may cause progression of liver disease to cirrhosis,[150] endocrine organs damage such as hypothyroidism, parathyroid insufficiency, and DM,[151] and cardiac abnormalities such as cardiomyopathy, one of the main causes of mortality in treated thalassemia major young adults.[152] Nevertheless, a prospective study and a meta-analysis showed no statistical association of liver iron concentration with mortality after allogeneic HSCT.[153,154] Post-transplant monitoring of iron overload should aim to evaluate function of primary organs (brain, heart, lungs, kidneys) and minimize iron burden in order to improve outcome.[30,149] Therapeutic management by phlebotomy or iron chelation therapy in case of anemia precluding phlebotomy should aim to reach acceptable hematocrit (>35%) and ferritin (<1000 ng/mL) levels.[155]

## Neurological Complications

Neurologic complications occur frequently, and their etiology is multifactorial. Several drugs including cytotoxic

agents in the conditioning regimen, TBI, CNIs, and anti-infective drugs may have neurotoxic side effects.[156] Moreover, prior cranial irradiation, high-dose methotrexate, novel biologic agents or intrathecal therapy (IT), older age, and renal impairment may increase the risk of neurotoxicity.[157]

Fludarabine has been associated with dose-related neurotoxicity with cognitive impairment, progressive deterioration of vision, seizures, ataxia, and coma in severe cases.[158–160] The onset of toxicity was acute in most patients but at lower doses, as used in conditioning regimens, toxicity can be delayed. Progressive toxic leukoencephalopathy with central nervous system (CNS) demyelination may represent a late fludarabine toxicity.[161,162] Brain MRI shows diffuse white matter abnormalities in T2-weighted sequences. Neuropathologic examination demonstrates a severe leukodystrophy, diffuse demyelination with prominent macrophage infiltrate.[163–165]

CNIs are associated with major neurologic side effects that normally occur shortly after transplant.[166] Many published case series reported a posterior reversible encephalopathy syndrome (PRES) consisting of a neurologic syndrome characterized by confusion, deterioration of vision, seizures confirmed by the presence of multifocal edema involving the white matter of the parietal and occipital lobes at neuroimaging.[167] This is a reversible condition after CNIs suspension. Rare persistent neurologic deficits have been reported.[168,169]

Some reports have also described a tacrolimus-related delayed chronic leukoencephalopathy and demyelinating peripheral polyneuropathy, resembling chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).[170–172] Some antibiotics (eg, aminoglycosides) and loop diuretics, in addition to CNIs, TBI, and platin compounds may cause neurosensory toxicity, as well hearing damage and taste dysfunction (as reported above),[173] which could lead to a long-term disability and compromise QoL.

Central and peripheral neurological manifestations of cGvHD are rare. Manifestations affecting the peripheral nervous system (PNS) include polymyositis, myasthenia gravis (MG), and Guillain-Barrè-like demyelinating polyneuropathy, starting generally from several months to years after allogeneic HSCT.[156] Polymyositis was reported to occur in about 2–3% of patients, whereas immune neuropathies and MG occur in less than 1% of them.[174,175]

A case report and literature reviews from 20 articles published between 1990 and 2016 found 39 reported cases of CNS GvHD. Median symptoms onset was 385 days after HCST and neurologic presentation was highly variable, mainly represented by immune-mediated encephalitis, cerebrovascular manifestations, or demyelinating disease as seen in relapsing/remitting multiple sclerosis.[176] Diagnosis of neurological manifestations can be highly challenging and remains associated with dismal prognosis, significant morbidity, and reduced QoL. Early diagnosis and treatment are crucial to avoid long-term impairment and disabilities.

In addition to CNS and PNS toxicity, many patients suffer from cognitive impairment, associated with risk factors such as high-dose chemotherapy, use of TBI in conditioning, and IST.[177] The most common symptoms are reduced concentration, verbal recall and fluency, as well as impaired fine motor dexterity.[178,179]

A prospective observational study conducted on 477 allogeneic HSCT recipients reported that 3 years after transplant 35.7% of patients demonstrated global cognitive deficits. MAC HSCT recipients had significantly worse cognitive functioning for executive function, verbal speed, processing speed, auditory memory, and fine-motor dexterity, while RIC HSCT recipients showed a delayed decline, highlighted only 3 years after HSCT. Older age, male sex, lower education and income, and pre-transplant cognitive reserve were associated with post-transplant cognitive impairment.[180]

Neurocognitive deficits following transplant represent a significant barrier to societal reintegration, bringing ulterior psychosocial distress and anxiety to many patients, depending upon the impact on daily activities and reintegration. The introduction of less toxic conditioning regimens has allowed expansion to more fragile and elderly patients, who are more susceptible to the development of neurocognitive impairment.[181] Transplanting older recipients may also mean a reduced physical strength and reduced social support which makes patients more prone to fatigue and development of social isolation.

## Skeletal Complications

Osteoporosis and avascular necrosis are the major complications. Osteoporosis and fracture risk were reported in up to 50% of patients. Several causes such as chemotherapy, RT, corticosteroids therapy, use of CNIs, hypogonadism, vitamin D deficiency predispose to osteoporosis. Bone loss generally occurs 6–18 months after HSCT.[63,85] Baseline evaluation is recommended for all patients at the start of the LTFU program. Dual X-Ray Absorptiometry (DEXA) scan is indicated to assess lumbar and femoral bone mineral density (BMD). If normal, no subsequent reassessments are needed. Preventive measures to prevent bone

loss are adequate vitamin D and calcium intake (with food intake or supplementation), physical exercise, and no smoking. Bone antiresorptive drugs should be used when fracture risk (assessed with validated algorithm such as FRAX or DeFRA) is high or when corticosteroid treatment is continued for over three months at a prednisone equivalent dose >5 mg per day. Currently, bisphosphonates or denosumab are available treatments.[182]

Avascular necrosis affects 4–19% of transplanted patients and usually occurs around 5 years after HSCT. It typically affects femoral heads, causing severe bone degeneration and acute local pain. TBI, corticosteroid and CNI treatments, and older age are risk factors.[63] When diagnosis is suspected, MRI should be performed, and early orthopedic evaluation is recommended.

## Infectious Disease

Proper immune reconstitution contrasts disease recurrence and infectious complications. NK-cells are the first lymphocyte subset to recover, followed by $CD8^+$ T-cells, which often reach supernormal levels within 2–8 months after HSCT. Later, B-cells and eventually $CD4^+$ T-cells recover.[183,184] Overall, T-cell reconstitution occurs in two distinct phases. The initial phase is thymus-independent with the peripheral antigen-driven expansion of donor T cells and a skewed T-cell receptor (TCR) repertoire followed by a thymus-dependent expansion of naïve T cells derived from donor cells with a more expanded TCR repertoire.[185,186] However, recipients may show little or no thymic-dependent T-cell regeneration for months to years as the thymus may be damaged by therapy and cGvHD. Detection TCR excision circles (TRECs) in the blood are a reliable marker of thymic output[187–189] and may be persistently low up to 20 years after transplant.[190–193]

The severity of cGvHD significantly correlates with the degree of immunosuppression and the risk of infectious complications given the damage of the lymphoid microenvironment, the adverse effects on homeostatic peripheral expansion, and the prolonged immunosuppression that hampers a robust reconstitution of the immune function of both the T and B cell compartments. Other factors that predispose to infections are age, comorbidities, and the exposure to pathogens prior to transplant. Extensive cGvHD and TBI containing conditioning regimens are major risks for bacterial infection.[194] For this reason, patients should be educated about their immune status and the recognition of warning symptoms of infection to timely seek early medical attention. Further suggestions about environmental risks, safe sex, water and food safety, and travel safety have been included in specific guidelines,[195] which, however, cover mainly the early post-transplant course.

For at least one year post-transplant or until 3–6 months after IST is discontinued whichever occurs first, all patients should receive prophylaxis against *Pneumocystis jirovecii* with trimethoprim-sulfamethoxazole (or dapsone or atovaquone in allergic/intolerant patients) and Varicella Zoster Virus (VZV) with acyclovir.[63] Some experts recommend antibiotic prophylaxis before dental care in patients with indwelling central venous catheters (CVC).[30] Administration of prophylactic antibiotics for oral procedures should follow the American Heart Association (AHA) guidelines for endocarditis prophylaxis.[196] GvHD and long-term use of corticosteroids have been a major risk factor associated with the onset of invasive fungal infection (IFI).[197]

Given the loss of immunity to various pathogens during the first few months post-transplant, re-vaccination is highly recommended irrespective of the pre-transplant donor/recipient vaccinations. Vaccination with inactivated vaccines is safe and is an effective way to re-establish protection against several pathogens (eg, *Influenza* virus, *Streptococcuspneumoniae*, and *Haemophilus influenzae*). Response to vaccines in transplant patients is usually lower than in healthy individuals of the same age, but it improves over time to become close to normal at 2–3 years post-transplant in the absence of major complications. However, because immunogenic vaccines have been found to induce a response in a substantial proportion of the patients as early as 3–6 months post-transplant, early vaccinations with inactivated vaccines have recently been recommended irrespectively of the presence/absence of GvHD and/or treatment with immunosuppressants.[198] However, different recommendations are reported for varicella and measles, mumps, and rubella attenuated vaccines which are recommended only after 24 months from transplants in seronegative patients with no GvHD, no IST, no relapse, and no recent administration of immunoglobulins.[198,199] Overall, a life-long surveillance is mandatory in these otherwise cured patients.

## Underlying Disease Recurrence and Post-Transplant Malignancies

Recurrence of the underlying disease is currently the main cause of treatment failure and mortality given that up 40–45% of patients transplanted from an HLA-identical sibling and up to 35% from an unrelated donor will eventually

relapse.[200–202] Overall, most relapses occur within the first 2 years from transplant, although a later relapse incidence of about 10% persists.[6] Long-term disease follow-up will depend on the type of underlying malignancy. Ideally, only patients in prolonged CR without maintenance treatment may avoid hematologic consultations. Table 1 summarizes suggestions/recommendations for disease-specific LTFU.

However, several reports on pediatric and adult cohorts have shown that the cumulative incidence of secondary malignancies at 10 years ranges from 1% to 11%. These figures appear on the rise without reaching a plateau,[203–206] and, globally, post-transplant neoplasms are the cause of death in 2% to 10% of long-term survivors.[207] Transplant patients are at higher risk of developing a secondary malignancy compared with their age-matched peers, with a 3-fold higher risk at ≥15 years post-transplant.[115,208] MAC regimens containing high-dose alkylating agents[209] and TBI,[80,210] likely combined with a susceptible genetic background, immunodeficiency, and GvHD,[211] are well-established risk factors. RIC may reduce partly but not completely this risk.[120,204,206,212]

Secondary malignancies can be classified into post-transplant lymphoproliferative disorders (PTLD), hematologic malignancies, and solid tumors. PTLD, often EBV-related, usually occur within the first year after transplant.[213] Pre-emptive treatment for EBV reactivation is currently common.[30] Secondary MDS and acute myeloid leukemia (AML) may recur years after transplant[214] while solid tumors are the latest malignancies to be diagnosed.[115,203] Organs often involved are the skin, GI mucosae (especially oropharynx, see section 4.4), and thyroid. TBI is associated with breast and thyroid cancers.[215] Five-year overall survival (OS) varies from 88% to 100% for thyroid, testis, and melanoma, to ≤20% for bone, lower GI tract, and CNS tumors.[216]

Cancer screening is recommended as for general population (Table 2). Preventive measures should include avoidance of exposure to ultraviolet radiation[217] and smoking cessation. Some studies have evaluated the role of HPV in the pathogenesis of SCC after HSCT,[218,219] but prospective studies are needed to confirm emerging evidence about the efficacy of HPV vaccination in its prevention.[220]

**Table 1** Suggested Hematologic Malignancies Follow-Up After Persistent Complete Remission Achievement

| Disease | Suggested Follow-Up |
|---|---|
| Aplastic anemia and other non-malignant diseases | • annual CBC |
| Lymphoma and chronic lymphocytic leukemia | • annual chest X-Ray (if symptoms or previous localization) and abdomen US in indolent lymphomas, up to 5 years after HSCT, then only if clinically indicated<br>• periodic peripheral lymph nodes palpation for all others[223] |
| Acute leukemia, myelodysplastic and myeloproliferative syndromes | • annual CBC<br>• bone marrow examination with search for minimal residual disease up to 5 year after HSCT (3, 6, 12, 18, 24 months after HSCT, annual after second year post-transplant) |
| Multiple myeloma | • serum protein electrophoresis, serum free-light chain ratio, urine and serum immunofixation every 6 months<br>• imaging only if symptoms |

**Abbreviations:** CBC, complete blood count; US, ultrasound; HSCT, hematopoietic stem-cell transplant.

## Models for Long-Term Follow-Up

Until recently, "transplant doctors" have dealt with the care of long-term survivors on their own. However, the wide spectrum of transplant complications and late effects make appropriate care rather difficult for a single health-care provider. Thus, efficient survivorship care should be considered a multidisciplinary approach requiring interactions among oncologists, hematologists, pediatricians (for childhood cancer survivors), internists, and nurses, and many other specialists. This team should follow the survivors lifelong, and it is very important that all team members have specific knowledge and expertise of physical and psychological late effects that can arise after HSCT.[28,30]

Different LTFU models have been proposed to satisfy the specific needs of HSCT survivors. The main difference between models is that some are focused on the survivorship care of only HSCT survivors, others are designed for survivors of various types of cancer, including HSCT recipients.

The latter is most commonly employed for LTFU programs involving cancer survivors transplanted during childhood and represents a good example of collaboration among oncologists and physicians with different areas of expertise, though transplant specialists should invariably be involved in the management of transplant issues such as GvHD and its related complications.

**Table 2** Suggested Cancer Screening Program

| Tumor Type | Recommended Screening[a] |
|---|---|
| Non-melanoma skin cancer and melanoma | • reduce UV skin exposure<br>• periodic self-evaluation<br>• annual dermatological evaluation |
| Thyroid cancer | • periodic neck palpation<br>• if using US, 5 years after RT and then once every 3–5 years if negative |
| Breast cancer | • annual clinical evaluation<br>• annual mammography/mammary MRI starting at 25 yo or 8 years after radiation, whichever occurs later, but no later than age of 40 |
| Pulmonary cancer | • avoid/stop smoking |
| Oropharynx cancer | • annual dentist evaluation |
| Colorectal cancer | • annual FOB testing<br>• colonoscopy once every 5 years, starting 10 years after abdominal RT, however not before age of 40<br>• rectosigmoidoscopy once every 5 years in >50 yo patients |
| Prostatic cancer | • periodic serum PSA level testing as indicated in general population |
| Cervix cancer | • Pap-test once every 1–3 years in >21 yo women |
| Hematologic disorders | • annual CBC, hematologic visit if abnormal |
| Other sites | • as per clinical indication/monitoring |

**Note:** [a]Use proper diagnostic tools if indicated as for good clinical practice.
**Abbreviations:** UV, ultraviolet; US, ultrasound; RT, radiotherapy; MRI, magnetic resonance imaging; FOB, fecal occult blood; PSA, prostatic specific antigen; CBC, complete blood count; yo, years old.

Otherwise, the models focused only on HSCT survivors usually provide an excellent management of specific complications in transplanted patients (first of all GvHD), but generally these clinics are difficult to establish, unless in large transplant centers.

## Conclusions and Future Directions

To set-up an LTFU clinic capable of meeting the needs of HSCT survivors, a wide range of different specialities should be considered. The right time for the transition should be established by the primary transplant physician and in particular for pediatric patients before they reach adulthood. To ensure continuity of care, a close cooperation between the LTFU clinic and the transplant physicians is a fundamental requirement. Moreover, the definition of specific roles and the identification of a leading coordinator in the LTFU team are essential to avoid overlapping and better allocate resources. The team leader does not necessarily have to be the transplant physician as other specialists (ie, internists, endocrinologists, or hematologists/oncologists)[28,30,221,222] may play this crucial role. Individualized written survivorship care plans that include treatment information and recommendations for monitoring transplant late effects are of great value for both the patients and care specialists who manage surveillance programs.[28,222] The longer the follow-up, the higher the possibility that patients may also be followed by primary care/family physicians, who should gradually be involved in the LTFU of their patients under the supervision of the LTFU team. Good communication and interaction between primary health providers and the LTFU team are becoming more and more important given the increasing age of HSCT survivors that may predispose them to a faster aging process. Furthermore, given the increase in long-term transplant survivors, the focus of clinical care will inevitably require more and more efficient and standardized LTFU programs.

In conclusion, given that many centers do not currently have dedicated LTFU clinics,[28,221] it is desirable that in the near future most transplant programs will include a multidisciplinary approach for long-term survivors.

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## Author Contributions

LG, FF, EB, BB designed the review. All authors made substantial contributions to conception, contributed towards data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. EB and BB supervised manuscript writing.

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The authors declare no potential conflicts of interest relevant to the article.

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