Late effects in patients treated with HSCT

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1. Introduction
With increasing number of transplants performed yearly, and improvement in outcome, long-term survivorship of patients treated with HSCT has become increasingly important. The main aim of the HSCT is still to cure the primary disease. However, long-term survivors expect to return to normal health, with adequate physical and psychological functioning and social integration in the family and at work, as well as subjective well-being. Despite improvement in the results of HSCT, the proportion of patients surviving two years after HSCT is decreased when compared to a matched general population, and after allogeneic HSCT death rate remains higher than expected even more than 20 years after transplantation. This higher death rate is necessarily associated with increased morbidity.

2. General aspects of long-term survivorship
The likelihood of long-term survivorship depends on the patient’s characteristics (age, gender, comorbidity before HSCT), the primary disease, its risk category and remission status before transplantation, the conditioning regimen (MAC, RIC, use of TBI), the cell source (bone marrow, mobilised peripheral stem cells, umbilical stem cells), as well as the onset of GvHD and the drugs used for its treatment in patients receiving allogeneic HSCT (1, 2).
The pattern of late effects after HSCT may change over time. One reason is the change in practice regarding the conditioning regimen and the transplant procedure. While TBI was universally used for more than two decades, today non-irradiation protocols and RIC conditioning regimens have become established. Therefore, cataract, which was an almost universal late complication after HSCT, has been decreasing in frequency over the last decade. On the other hand, the increasing age of the patients receiving allogeneic HSCT, as well as more frequent use of an alternative donor, has led to an increased incidence of late effects related to chronic GvHD and its treatment. Accordingly, the incidence of late avascular necrosis of the bone and chronic kidney disease may increase. Although TBI may no longer form part of standard condition regimens, the knowledge of its late consequences is mandatory, because patients who received TBI many years ago remain at risk of radiation-related late effects. Indeed, some radiation-related late effects, such as non-squamous solid tumours or cardiovascular complications are very late effects appearing more than 10 or even 20 years after HSCT, and will therefore continue increasing during the next decades.
Late effects may be the direct consequences of the transplantation procedure and its conditioning regimen. Typical examples are cataract formation, infertility or
secondary malignancies. It has also become apparent that there may be secondary late effects, occurring as the consequence of a primary late effect or its treatment. Osteoporosis and dental caries are such secondary late effects, while post-transplant osteoporosis is in part the consequence of gonadal failure occurring after TBI and may also result from steroid treatment of chronic GvHD. Likewise, dental caries occur in patients with decreased salivary flow, due to conditioning with TBI and/or chronic GvHD. Cardiovascular events after HSCT have emerged as very late effects, and can be considered as tertiary late effects, due to the increased incidence of cardiovascular risk factors appearing after HSCT (secondary late effects), which are in turn the consequence of primary late effects, such as gonadal insufficiency, insulin resistance and/or growth hormone deficiency after HSCT.

Late effects are defined as those that occur after the first three months post-transplant and provoke health restriction during long-term survivorship. They are usually divided into non-malignant and malignant late effects. In fact, any organ and any tissue can be the target of a late effect. The chapter will focus on practical screening and management issues of non-malignant and malignant late effects (3, 4). Each of the main late effects will be discussed systematically in four parts: 1. scientific background and risk factors, 2. clinical presentation and diagnosis, 3. prevention, 4. treatment.

3. Late ocular effects
There are two main non-malignant late effects, cataracts and kerato-conjunctivitis.

3.1 Scientific background and risk factors
Cataracts are closely related to TBI and to a lesser extent to the use of steroids. With single dose irradiation of $\geq 10$ Gy the probability of cataract is up to 80% or more. Fractionation of the dose and lower dose rate greatly reduced the risk of cataract to 30% at 3 years. With a conditioning regimen of cyclophosphamide alone or busulfan and cyclophosphamide the risk is about 20% at 5 years.
Kerato-conjunctivitis sicca syndrome is part of a global sicca syndrome affecting ocular, oral, anal and genital mucosa. These manifestations are closely related to chronic GvHD, which may lead in its most extensive form to a Sjögren-like syndrome. The cumulative incidence of late-onset kerato-conjunctivitis sicca syndrome is 20% by fifteen years after HSCT. It reaches nearly 40% in patient with chronic GvHD, but is less than 10% in those without GvHD.

3.2 Clinical presentation and diagnosis
Cataracts usually develop gradually, and are painless. Symptoms include decrease
in vision, particularly in bright or low light, as well as decreased contrast, and altered colour appreciation. The diagnosis is made by slit lamp examination. The ocular manifestations of kerato-conjunctivitis sicca syndrome include reduced tear flow, dryness and irritation of the eyes, sterile conjunctivitis, corneal epithelial defects, and corneal ulceration. The diagnosis can be confirmed by Schirmer’s test.

### 3.3 Prevention
The risk of cataracts can be greatly reduced by the use of a non-radiation conditioning regimen, or by fractionation of the TBI, as well as by reduced use of steroids. General hygiene measures help to prevent superinfection in kerato-conjunctivitis sicca syndrome.

### 3.4 Treatment
The only treatment for cataract is to surgically remove the opacified lens from the eye to restore transparency of the visual axis. Today, cataract surgery is a low risk procedure and improves visual acuity in 95% of eyes that have no other pathology. The treatment of isolated kerato-conjunctivitis of the eye is based on the management of chronic GvHD with regular use of topical lubricants. Virus or bacterial infections have to be treated promptly and adequately. If the ocular manifestation is part of an extensive chronic GvHD, systemic treatment must be instituted.

### 4. Skin and appendages
Non-malignant late effects may involve skin, nails, and hair.

#### 4.1. Scientific background and risk factors
Sustained involvement of the skin, including mucosal and skin appendages (nails and hair) is common after allogeneic HSCT and is most often related to chronic GvHD. Persistent cutaneous lesions play a central role in late morbidity and quality of life in long-term survivors. Cutaneous GvHD can develop spontaneously, or can be triggered by events such as UV irradiation, physical trauma, or infections.

#### 4.2 Clinical presentation and diagnosis
Dryness of the skin is a frequent early manifestation of chronic GvHD. Chronic cutaneous GvHD may present as lichenoid or sclerodermaid GvHD. In the lichenoid form, the skin is usually intact and presents as dry skin, pruritus, rash, dyspigmentation, or a lichen planus-like eruption. Chronic sclerodermaid GvHD can lead to more disabling skin complications with ulcerated areas, which are prone to
superinfections, and sclerotic changes of the subcutaneous tissues. In advanced cases sclerosis provokes functional impairment with severe joint contractures. Nail dystrophy, longitudinal ridging, nail splitting or nail loss are distinctive signs of chronic GvHD. Scalp alopecia, loss of body hair, and premature greying are all characteristics of chronic GvHD, but these findings are not diagnostic. The diagnosis of cutaneous chronic GvHD is usually based on clinical examination. Histological examination may support the diagnosis.

4.3 Prevention
Patients should be encouraged to reduce direct UV skin exposure. Photoprotection including protective clothing and high-potency sun-screen should be used and direct-exposure to sunlight should be avoided.

4.4 Treatment
Limited lichenoid GvHD lesions may respond to topical corticosteroids and calcineurin inhibitors as well as to phototherapy. Systemic immunosuppressive treatment is necessary in case of more advanced disease. In addition to the immunosuppressive treatment, early physiotherapy with stretching becomes essential, in order to prevent contractures and to improve range of motion.

5. Oral and dental complications
There are a number of non-malignant late effects of the oral cavity, including dental complications.

5.1 Scientific background and risk factors
Late oral complications are strongly associated with chronic GvHD and conditioning with TBI. They are characterised by mucosal atrophy, erythema, lichenoid-hyperkeratinoid lesions, salivary gland dysfunction, taste disorders, and dental complications. Late sclerotic changes may result in decreased oral opening. Saliva plays a major role in maintaining oral health. Abnormal salivary composition and reduced salivary flow can be the consequence of TBI and/or chronic GvHD. In long-term survivors, salivary gland dysfunction is associated with an increased risk of rampant dental decay. Poor oral hygiene associated with oral discomfort is an additional contributing factor.

5.2 Clinical presentation and diagnosis
The symptoms most often reported are pain, sensitivity to normally tolerated items, and xerostomia. Secondary oral infections, such as candidiasis, herpes simplex and cytomegalovirus can complicate and exacerbate oral lesions. Painful
mucosal ulcers hinder normal food ingestion. Rampant dental decay may occur in patients with sicca syndrome, poor dental hygiene and large-scale consumption of sugar-containing food or drinks.

5.3 Prevention
Maintaining oral and dental health is critical. Basic oral care include brushing of teeth with a soft toothbrush twice a day, the use of fluoride-containing toothpaste, daily flossing between teeth and under any bridges, the use of remineralising solutions, and avoidance of regular sugar-containing beverages.

5.4 Treatment
Topical corticosteroids such as budesonide mouthwash may be used as adjunctive therapy for oral GvHD. Systemic treatment of chronic GvHD is usually required. Regular dental review is important.

6. Thyroid dysfunction
Endocrine dysfunction is a frequent non-malignant late effect on the thyroid gland (5).

6.1 Scientific background and risk factors
Thyroid dysfunction is frequent, appearing within the first 2 to 3 years after HSCT. TBI plays a key role, and the risk of thyroid dysfunction depends on the dose and type of irradiation. The risk is 5–6 time higher when single dose instead of fractionated TBI is applied. The incidence after conditioning with busulfan and cyclophosphamide is 11%. The median time to diagnosis of hypothyroidism is about 4 years after HSCT.

6.2 Clinical presentation and diagnosis
Asymptomatic compensated hypothyroidism with increased TSH and normal fT4 levels is the most common form of thyroid dysfunction. In some patients these will normalise spontaneously. Overt hypothyroidism is variable and depends on the risk factors to which the patient has been exposed. Autoimmune diseases such as Hashimoto’s thyroiditis and Graves’ disease due to adoptive transfer or chronic GvHD have been reported. Yearly screening of TSH is indicated in patients at risk for thyroid dysfunction (previous radiation therapy of the neck, TBI), or if relevant symptoms develop.

6.3 Prevention
The use of a non-TBI conditioning regimen is the only preventive measure.
6.4 Treatment
Patients with overt hypothyroidism should receive hormonal substitution. Periodic adjustment of the dose, based on thyroid assessment, should be done with the help of an endocrinologist. Treatment of asymptomatic hypothyroidism remains controversial, but should be considered if TSH levels remain high or increase.

7. Fertility and gonadal dysfunction
Non-malignant late effects due to gonadal damage include endocrine dysfunction and infertility (6, 7).

7.1 Scientific background and risk factors
Gonadal damage after HSCT is dependent on the age of the patient, the dose and schedule of TBI, and the use of chemotherapy. Ovaries are more vulnerable than testes. In female patients, infertility and hyper gonadotrophic hypogonadism is almost universal after TBI, with elevated serum FSH and LH. Fractionation of TBI has a sparing effect on the ovaries. Busulfan is one of the most gonadotoxic chemotherapeutic agents. In contrast, conditioning with cyclophosphamide alone is associated with a high probability of recovery of gonadal function and fertility. The age at transplantation is of major significance: the younger the age, the better the chances for gonadal recovery.
In male recipients, endocrine dysfunction of the testis is less pronounced. Testosterone levels are usually normal, since the Leydig cells are more resistant to chemotherapy and irradiation than the Sertoli cells. Usually serum FSH levels are increased, but with normal LH levels. The absence of spermatozoa is a common long-term sequel in male patients receiving chemotherapy and irradiation prior to HSCT. Azoospermia is less frequent in patients conditioned with busulfan and cyclophosphamide (50%) and is uncommon in patients treated with cyclophosphamide alone (10%). Even when conditioned with standard dose TBI, male recipients surviving more than 10 years, younger than 25 years at HSCT, and without chronic GvHD have a reasonable likelihood of spermatogenesis.

7.2 Clinical presentation and diagnosis
In young adult women gonadal dysfunction leads to a premature menopausal state after HSCT with menopausal symptoms. Untreated gonadal failure can in long-term survivors lead to secondary late complications, such as osteoporosis and metabolic syndrome. Male HSCT recipients are usually asymptomatic. Symptoms suggestive of hypogonadism are erectile dysfunction, low libido and bone loss. Females in whom hormonal substitution is discontinued should be assessed regularly for FSH and LH.
7.3 Prevention
The impact of treatment on fertility and symptoms due to gonadal failure must be discussed with patients before HSCT and repeatedly throughout the treatment period after HSCT. In young women healthcare providers should provide menopause-related symptoms and management of menopausal issues. Consideration should be given to sperm or embryo preservation before HSCT. Paradoxically, the potential recovery of spermatogenesis should also alert staff about the need for counseling regarding birth control during post-transplantation follow-up.

7.4 Treatment
The main reason to treat hypogonadism after transplantation is the prevention of osteoporosis and prevention of symptoms in pre-menopausal-aged women. Up to 90% of adult female patients require sex-hormone replacement therapy after HSCT. This replacement therapy can be interrupted every 1-2 years to evaluate spontaneous recovery. Sex-hormone replacement will not be necessary in most of the male patients, despite reduced or absent spermatogenesis.

8. Noninfectious respiratory tract complications
Non-malignant late effects of the lung (8) include obstructive and restrictive problems.

8.1 Scientific background and risk factors
Late-onset non-infectious pulmonary complications involving both the airway and lung parenchyma are frequent after HSCT, appearing usually between 3 months and 2 years post-transplant; however, functional consequences may persist for years. The most common delayed pulmonary complications include bronchiolitis obliterans (BO), cryptogenic organising pneumonia (COP), and idiopathic pneumonia syndrome (IPS). BO is a severe obstructive pulmonary manifestation characterised by a nonspecific inflammatory injury affecting primarily the small airways. In advanced stages, due to the progressive peri-bronchiolar fibrosis, restrictive functional changes also develop. BO is considered as the main pulmonary manifestation of chronic GvHD. COP is a clinico-pathological syndrome involving bronchioles, alveolar ducts, and alveoli and presents as a restrictive respiratory complication. COP appears mainly between 1 and 12 months post transplant, with an incidence of <2%. There is a strong association between COP and GvHD. IPS usually occurs within 120 days after transplantation and is associated with TBI, GvHD, and older age at HSCT. Patients conditioned with busulfan and cyclophosphamide have lower rates of IPS. Delayed-onset IPS occurring years after HSCT has been reported.
8.2 Clinical presentation and diagnosis
The clinical presentation of BO is usually insidious with dry cough, progressive dyspnea, and wheezing. In pulmonary function tests, a decline of >20% in FEV1 from the pre-transplant value, or <80% of the predicted FEV1 should alert transplant physicians. High resolution CT of the chest with inspiratory and expiratory phase images shows a characteristic mosaic pattern. The clinical presentation of COP is usually acute, with dry cough, dyspnea and fever. The chest X-ray presents peripheral patchy consolidation, ground glass attenuation and nodular opacities. Pulmonary function tests show a restrictive pattern. Bronchoalveolar lavage is recommended to rule out infection. The definitive diagnosis is based on histopathology. Regular pulmonary function tests should be performed regularly after allogeneic HSCT. If a decrease of the function tests is observed, further evaluation is warranted. IPS presents with pulmonary function tests showing a restrictive pattern. High resolution computed tomography shows a diffuse pulmonary parenchymal disease.

8.3 Prevention
Avoidance of smoking tobacco should be recommended for all patients.

8.4 Treatment
For the treatment of BO and COP corticosteroids should be started without delay. Other treatment for chronic GvHD may be required. Prophylaxis for VZV and PCP should be continued. Bacterial and fungal infections have to be treated appropriately. There is no specific treatment for IPS.

9. Late cardiac complications
Non-malignant late effects of the heart may lead to heart failure (9, 10).

9.1 Scientific background and risk factors
Experiences of cancer survivorship in the non-transplant setting may anticipate the magnitude of risk in patients treated with HSCT. In long-term survivors with Hodgkin’s lymphoma, the risk of cardiac failure is 3 to 5 times increased compared to an age-matched general population. Pre-transplant anthracycline exposure and the presence of post-transplant comorbidities are the main risk factors for late cardiac failure after HSCT. Conditioning-related chemotherapy does not contribute significantly to late cardiac complications.

9.2 Clinical presentation and diagnosis
Dyspnea on exertion is the most common presenting symptom, followed by fatigue, orthopnea and weight gain. Routine cardiac surveillance and screening may be of
limited value. However, patients at risk, and those with symptoms should be monitored clinically. ECG should be performed and extended cardiac investigation including echocardiogram should be discussed with a cardiologist.

9.3 Prevention
Cardiac disease occurs 10 years or later after treatment. This means that these effects are slow to develop, and may be partially prevented with the control of other cardiovascular risk factors, including arterial hypertension. Endocarditis prophylaxis in patients with valvular anomaly is recommended.

9.4 Treatment
Heart failure should be managed as for non-transplant patients.

10. Late vascular complications
Non-malignant vascular late effects include cerebrovascular and cardiovascular disease (11, 12).

10.1 Scientific background and risk factors
The cumulative incidence of an arterial event, such as cerebrovascular, coronary artery or peripheral arterial disease is 22% at 25 years after allogeneic HSCT. It is higher after allogeneic than after autologous HSCT, supporting the hypothesis that the alloreactive transplant is involved in the atherosclerotic process. The established cardiovascular risk factors appearing after HSCT (hypertension, dyslipidemia, diabetes, smoking, physical inactivity) are the main risk for a premature late cardiovascular complication post-transplant.

10.2 Clinical presentation and diagnosis
The clinic manifestations of late cardiovascular complications after HSCT are similar to those observed in a general population. However, the events may occur at an earlier age that expected. Cerebrovascular disease may present as transient ischaemic attack, stroke or symptoms related to lacunar infarcts of the brain. Clinical manifestations of coronary artery disease are angina pectoris, myocardial infarction, and symptoms due to chronic coronary heart disease. Patients with peripheral arterial disease can present with claudication, rest pains, acute ischemia or gangrene. Silent myocardial infarction is not uncommon, due to the possible damage of the autonomous nervous system.

10.3 Prevention
Control of cardiovascular risk factors is the main focus of preventive measures, and
starts with education and counseling for a heart-healthy lifestyle. Patients should be encouraged to undertake regular physical activity, stop smoking tobacco, avoid passive smoking and maintain a healthy body weight. Proper management of cardiovascular risk factors should be started early during follow-up, and not be postponed until the patient is off immunosuppression.

10.4 Treatment
Cardiovascular symptoms should undergo appropriate investigation and early treatment as for non-transplanted patients.

11. The metabolic syndrome in long-term survivors
Non-malignant late effects occurring in long-term survivors after HSCT include hypertension, dyslipidemia, and diabetes (13). As previously discussed, these predispose to vascular complications.

11.1 Scientific background and risk factors
Dyslipidaemia, hypertension, and diabetes occurring after HSCT and also physical inactivity and ongoing smoking are related to the increased risk of cardiovascular disease in long-term survivors. Two or more cardiovascular risk factors are associated with a more than 5-fold increase of late cardiovascular complications. Retrospective studies have reported a prevalence of diabetes mellitus to be between 7 and 13% after allogeneic HSCT. The prevalence of dyslipidaemia is even higher, ranging between 9 and 39%. The reason for the high prevalence after allogeneic HSCT is not yet well understood. It could be the consequence of prolonged and intensified immunosuppressive treatment, post-transplant, endocrine dysfunction or leptin resistance. However, the use of immunosuppressive treatment cannot explain alone the increase of these risk factors after allogeneic HSCT, since it is observed even in patients off immunosuppressive treatment.

11.2 Clinical presentation and diagnosis
Patients with abnormal cardiovascular risk factors are usually asymptomatic until a late cardiovascular complication occurs. Therefore, regular screening for cardiovascular risk factors should be included for all patients. Checking blood pressure at every clinic visit and measuring of fasting blood sugar and lipid profile at the yearly assessment are recommended. Efficacy of the treatment for a cardiovascular risk factor should be monitored adequately. Cardiovascular risk factors and particularly dyslipidaemia are undiagnosed and undertreated in long-term survivors. Treatment for cardiovascular risk factors should not be postponed until discontinuation of immunosuppressive treatment.
11.3 Prevention
Counseling for a heart-healthy life style (stop smoking; regular exercise; maintaining healthy weight; dietary counseling) to prevent cardiovascular risk factors has become an essential part of the long-term management. Patients should be encouraged to reduce modifiable risk factors such as obesity, to perform aerobic exercise, and to eat a well-balanced diet.

11.4 Treatment
Management should focus on controlling dyslipidaemia, diabetes and hypertension. Proper management of risk cardiovascular factors reduces the risk of a cardiovascular event and improves survival in a non-HSCT population, and will probably reduce morbidity and mortality in long-term survivors after HSCT. For the management of dyslipidaemia, ATP III guidelines (Adult treatment Panel III from the National Cholesterol Education Program, NCEP) should be applied. Patients with increased LDL-cholesterol and risk for cardiovascular disease should be treated with statins. Patients with elevated triglycerides should be treated appropriately.

12. Chronic kidney disease
A number of factors may lead to progressive loss of renal function and ultimately to end-stage renal disease (14).

12.1 Scientific background and risk factors
Chronic kidney disease is defined as a sustained decrease in glomerular filtration rate (GFR) below 60 mL/min/1.73 m². Among 1190 long-term adult patients who underwent HSCT and survived for ≥1 year, the estimated cumulative incidence of chronic kidney disease was 4.4% at 5 years, and 5.7% at 10 years after HSCT. Older age at transplantation, exposure to calcineurin inhibitors for GvHD prophylaxis or treatment, a diagnosis of multiple myeloma, and nephrotoxic drugs used before HSCT, during conditioning and in the early phase post-transplant are the main risk factors. In a large cohort study of 1635 patients treated with HSCT, a strong association was observed between acute and chronic GvHD and renal dysfunction. However, it is not possible to distinguish whether GvHD itself or its treatment is the major factor responsible for chronic kidney disease. Severe kidney disease, with GFR below 30 mL/min/1.73 m², has been reported in 3% of patients; and half of these have end-stage disease needing chronic dialysis. Nephrotic syndrome is a rare complication after allogeneic HSCT. It has been described in patients after discontinuation of cyclosporin and is thought to be a renal complication of chronic GvHD.
12.2 Clinical presentation and diagnosis
Most patients are asymptomatic, and chronic kidney disease remains unnoticed if renal function is not checked regularly. Blood pressure should be checked regularly and hypertension investigated immediately. Renal function should be evaluated at least once yearly after HSCT. Screening assessment should include blood urea nitrogen, creatinine, calculation of GFR, and urine protein analysis. Renal biopsy should be considered if there is persistent renal dysfunction of uncertain cause.

12.3 Prevention
The use of nephrotoxic drugs should be minimised in patients at risk for chronic kidney disease.

12.4 Treatment
Arterial hypertension should be managed aggressively. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are the treatment of choice for hypertension and chronic kidney disease. In end-stage chronic kidney disease dialysis may become indicated. Rare cases of successful of kidney transplantation after HSCT have been reported.

13. Liver complications and iron overload
Non-malignant late effects of the liver include viral hepatitis and chronic GvHD, and consequences of iron overload after HSCT (15, 16).

13.1 Scientific background and risk factors
The most common causes of late hepatic dysfunction after HSCT are chronic GvHD, iron overload, and viral infections. Several causes of liver disease may coexist in the same patient. Hepatitis B (HBV) and hepatitis C (HCV) infection may be asymptomatic or progress to fulminant hepatitis, chronic active hepatitis or cirrhosis. Before systematic HCV screening by PCR was introduced in 1990 the prevalence of hepatitis C infection was high. Today the risk of acquiring HBV or HBV infection from blood transfusion is greatly reduced. However, reactivation of HBV has been reported. Patient with HBV usually exhibit mild to moderate liver disease, and progression to cirrhosis is rare. The long-term outcome of HCV infected patients after HSCT is worse. Patients surviving more than 10 years after HSCT are at higher risk of chronic hepatitis, and earlier development of cirrhosis as compared to HCV infected patients without HSCT. Liver disease is seen in 90% of patients with chronic GvHD.
Iron overload due to multiple transfusions and increased iron absorption is common in long-term survivors. Iron overload may be associated with liver toxicity and organ
dysfunction. Elevated ferritin before transplant is related with increased transplant related mortality and GvHD, and iron overload increases the risk of infections, veno-occlusive disease and hepatic dysfunction.

13.2 Clinical presentation and diagnosis
Chronic HCV hepatitis is often asymptomatic during the first decade post-HSCT, with fluctuating transaminase levels. However, patients surviving more than 10 years after HSCT may present clinical manifestation of liver cirrhosis, and are at risk for hepatocellular carcinoma. Liver GvHD typically presents as cholestasis, with increased bilirubin or alkaline phosphatase, but it may also present as acute hepatitis and rarely progress to biliary cirrhosis. In all long-term survivors, liver function tests (total bilirubin, alkaline phosphatase, transaminases) should be performed at least once a year. For patients with known hepatitis B or C, monitoring of HbsAG and viral load by PCR is advised. Because of the unspecific presentation of chronic liver disease after HSCT, liver biopsy is often required. Iron overload can be assessed by measuring serum ferritin, and if indicated by liver biopsy. MRI is a very sensitive, non invasive method to assess iron overload.

13.3 Prevention
The use of hepatotoxic drugs should be limited in patients at risk for chronic liver disease. Abuse of alcoholic beverages should be avoided.

13.4 Treatment
Patients with chronic HCV infection should be carefully monitored because of the risk of an accelerated progression to cirrhosis. Data on HCV treatment after HSCT are scarce, but patients may benefit from combination therapy with ribavarin and pegylated interferon. New HCV-specific protease inhibitors have been recently developed; no data are available yet in HSCT survivors but caution on their use is advised given their haematological toxicities. Despite a clear correlation between iron overload and persistent hepatic dysfunction, the clinical consequences of therapeutic iron depletion in transplant recipients have not been extensively evaluated. Nevertheless, it is reasonable to treat patients with persistent high ferritin, over 2500 ng/L, or more than 7 mg/g dry weight liver iron for iron overload. Patients without anaemia can undergo therapeutic phlebotomy (450–500 mL every 6 to 8 weeks). Iron chelation with desferoxamine or desferasirox should be initiated for the other patients.

14. Late complications of bone
Non-malignant late effects after HSCT include avascular necrosis (AVN) of the bone and osteoporosis (17, 18).
14.1 Scientific background and risk factors
The incidence of AVN varies from 4 to over 10%. The mean time from transplant to AVN is 18 months. The main risk factors for AVN are the use of steroids (total dose and duration), and TBI, mainly with receipt of single doses of 10 Gy or higher or >12 Gy in fractionated doses. In a recent series involving more than 1300 patients at the City of Hope Hospital, the cumulative incidence of AVN at 10 years was 4% after autologous HSCT, 6% after allogeneic sibling donor HSCT, and 15% after unrelated donor HSCT. For allogeneic transplant recipients, male sex, primary diagnosis of Hodgkin’s lymphoma or multiple myeloma, presence of chronic GvHD and exposure to CSA, FK506, prednisone and MMF rendered patients at increased risk.

Osteopenia and osteoporosis are both characterised by a reduced bone mass and increased susceptibility to bone fracture. HSCT can induce bone loss via the toxic effects of TBI, chemotherapy, and hypogonadism. The cumulative dose and number of days of glucocorticoid therapy and the number of days of cyclosporin or tacrolimus therapy showed significant associations with loss of bone density. Non-traumatic fractures occurred in 10% of patients. Nearly 50% of the patients have low bone density, a third have osteopenia and roughly 10% have osteoporosis, 12–18 months post-transplant.

14.2 Clinical presentation and diagnosis
Pain is usually the first sign of AVN of the bone. Early diagnosis can rarely be made using standard radiography and MRI is the investigation of choice. The hip is affected in over 80% of cases, with bilateral involvement in 60% cases. Other locations include the knee, wrist and ankle.

Osteoporosis remains often asymptomatic until the moment a fracture of the bone occurs. Non-traumatic fractures may occur in 10% of the patients. The degree of reduction in bone mass can be quantified on dual photon densitometry.

14.3 Prevention
The best preventive measure for AVN of the bone is to reduce the dose and duration of steroid treatment. The application of a non-TBI conditioning regimen is an additional preventive measure.

Patients should be advised to take regular exercise. Preventive measures for osteoporosis must include sex-hormone replacement in patients with gonadal failure. Additionally, decrease of bone loss and therefore prevention of osteoporosis can be obtained by reducing the duration and dosage of steroid therapy. Elemental calcium intake as well as vitamin D should be initiated particularly in patients on chronic steroid treatment.
14.4 Treatment
Symptomatic relief of pain and measures to decrease the pressure on the affected joints are of value, but most adult patients with advanced damage will require surgery. The probability of total hip replacement following a diagnosis of AVN is approximately 80% at 5 years. While the short-term results of joint surgery are excellent in the majority (>85%) of cases, long term follow-up of the protheses is needed in young patients who have a long life expectancy. Treatment with bisphosphonate should be initiated in patients with proved osteopenia and osteoporosis. The duration of the treatment in long-term survivors after HSCT remains unclear. However, before starting treatment, dental assessment should be performed and treatment given if indicated, because of the risk of osteonecrosis of the jaw.

15. Late haematological malignancies after HSCT
Late malignant complications may occur in long-term survivors, including haematological malignancies (19).

15.1 Scientific background and risk factors
Three type of late haematological malignancies may be observed in long-term survivors: late relapse of the primary disease, therapy-related MDS/AML (t-MDS/AML) after autologous HSCT, and donor-type leukaemia after allogeneic HSCT. Relapse of a haematological malignancy usually occurs during the first two years after HSCT. The risk is higher after autologous than allogeneic HSCT and depends on the type of leukaemia, the risk profile and the state of the disease before HSCT. However, late relapse can be observed at any time after HSCT, with a decreasing probability with longer follow-up. In a cohort of 1475 long-term survivors, 241 deaths were observed after 2 years 29% of which were attributed to relapse of the primary malignant disease. Of the 70 deaths due to relapse, 67% occurred between the second and fifth year of follow-up, 27% in the next 5 years, and only 6% after 10 years from HSCT. Lymphoma patients treated with autologous HSCT are particularly at risk for t-MDS/AML. The cumulative incidence of t-MDS/AML at 10 years has been reported to be between 6.8 and 36%. The higher risk of t-MDS/AML, when compared to other indications such as breast cancer, multiple myeloma or germ cell tumors has largely been attributed to the extent of pre-transplant treatment. The use of alkylating agents and a higher number of chemotherapy courses before HSCT as well as prior radiotherapy contribute substantially to secondary MDS/AML in transplant recipients. In up-front transplantation relatively low rates of secondary t-MDS/AML have been observed. However the use of TBI as conditioning was associated with an increased risk of t-MDS/AML.
Donor-type leukaemia refers to leukaemia of donor cell origin after allogeneic HSCT. Although described more than 2 decades ago, most of the first reports probably involved relapse of the original leukaemia because the “donor” origin of the leukaemia was based on classical cytogenetics of leukaemic cells in a transplant setting with donor/recipient sex-mismatch, in which the origin of the leukaemia cells was demonstrated by sex chromosome typing. However we now know that loss of the Y chromosome and duplication of the X chromosome can occur in leukaemic cells. Thus nowadays only molecular proof of the donor origin can be accepted, most often using PCR of VNTRs. Using these stringent criteria malignancies of donor cell origin, although rare, do exist. A further complexity was recently demonstrated by a study from the Seattle group showing that malignancies could also be transmitted through the graft either at a premalignant stage or as a minimal clone undetectable before transplantation.

15.2 Clinical presentation and diagnosis
Relapse or a secondary leukaemia may present as asymptomatic peripheral blood changes or in contrast with the full clinical manifestation of a leukaemia. The presence of macrocytosis, abnormal dysplastic neutrophils, immature haematopoietic cells, cytopenia or blasts in peripheral blood should raise suspicion. In case of unexplained blood changes a full bone marrow investigation is indicated. Regular bone marrow aspiration to detect early relapse is not useful in patients with a long-term survivorship of more than 2 years after HSCT. The monitoring of a molecular marker present at primary diagnosis may be useful. However, in AML negativity for a marker in peripheral blood does not exclude early relapse in the bone marrow, while the reappearance of a marker should arouse attention and initiate further investigations.

15.3 Prevention
There are few measures to prevent relapse, secondary MDS/AML or the appearance of donor-type leukaemia. In allogeneic HSCT immunosuppressive treatment should be tapered and stopped as soon as possible. Preemptive DLI infusions and the use of post-transplant maintenance treatment in high risk patients is currently under investigation. However its efficacy has still to be proven.

15.4 Treatment
The management of late haematological malignancies after HSCT depends on the time of appearance, the type of leukaemia, the extent of the disease and the comorbidity of the patient. Possibilities include stopping immunosuppressive treatment for patients still on immunosuppressive drugs, adoptive immunotherapy, re-transplant or experimental treatment.
16. Secondary solid tumors after HSCT
Late malignant complications in long-term survivors also include solid tumours (20, 21).

16.1 Scientific background and risk factors
Long-term survivors of HSCT have an increased risk of developing new solid cancers, with the risk rising from 2 to 6% at 10 years after transplantation. Several factors contribute to this increase, including TBI, primary disease, male sex, and pre-transplantation therapy. Chronic GvHD and immunosuppressive therapy have also been shown to contribute to excess risk, particularly for squamous cell carcinomas of the buccal cavity and the skin.
The largest studies today include a multi-institutional cohort of 28,874 allogeneic transplant recipients with 189 solid malignancies. Overall, patients developed new solid cancers at twice the rate expected based on general population rates, with the risk increasing over time; the risk reached 3-fold among patients followed for 15 years or more after transplantation. New findings showed that the risk of developing a non-squamous cell carcinoma following conditioning radiation was highly dependent on age at exposure. Among patients irradiated at ages under 30 years, the relative risk of non-squamous cell carcinoma was 9 times that of non-irradiated patients, while the comparable risk for older patients was 1.1. Chronic GvHD disease and male sex were the main determinants for risk of squamous cell carcinoma.
The probability of solid tumour type might be under-estimated, since some of them tend to develop very late after transplantation. Among 3,337 female 5-year survivors who underwent an allogeneic transplantation at the Fred Hutchinson Cancer Research Center or at one of 82 centres reporting to the EBMT, 52 females developed breast cancer at a median of 12.5 years following HSCT (standardised incidence = 2.2). Twenty-five-year cumulative incidence was 11.0%, and was higher among survivors who received TBI (17%) than those who did not receive TBI (3%). In multivariate analysis, increased risk was associated with longer time since transplantation, use of TBI, and younger age at transplantation. The hazard ratio for death associated with breast cancer was 2.5. Extrapolating from the existing data, it is likely the risk of solid cancers will continue to increase during the next decades.

16.2 Clinical presentation and diagnosis
Early detection of a secondary solid cancers is essential. At that time patients are usually asymptomatic. Regular self-examination and systematic yearly assessment allow early detection of secondary cancers of the skin, the oral cavity, gynaecological organs and the thyroid gland. Young female patients who received local irradiation
or TBI should have regular mammography from the age of 30 years or from 8 years post-transplant. Patients with head and neck irradiation should be regularly screened for thyroid gland abnormalities. In case of abnormal nodules, fine needle aspiration is recommended. Women, particularly those with chronic GvHD, should have a yearly gynaecological examination including a cervical smear. Patients with oral chronic GvHD should be regularly examined for secondary squamous oral cancers.

16.3 Prevention
Prevention is based on early detection of solid cancer. Therefore, patients should be counseled about the risk of late secondary cancers and shown how to perform self examination of the skin, the oral cavity and the breasts. Furthermore, patients should be advised not to expose themselves to active or passive tobacco smoking, and to avoid direct exposure of the skin to UV irradiation.

16.4 Treatment
Appropriate cancer management should be discussed with the specialised team.

References

Multiple Choice Questionnaire

To find the correct answer, go to http://www.esh.org/online-training/handbook/

1. The pattern may of late effects after HSCT changes over time, because
   a) Conditioning regimens are changing .................................................. ☐
   b) Fewer patients with CML are treated since the availability of tyrosine kinase inhibitors .................................................. ☐
2. **TBI is the main risk factor for**
   a) Late cardiac complications after HSCT
   b) Aseptic necrosis of bone
   c) Secondary cancer of the oral cavity
   d) Gonadal dysfunction in females

3. **GvHD is the main risk factor for**
   a) Cataract formation
   b) Bronchilitis obliterans syndrome (BOS)
   c) Secondary breast cancer
   d) Thyroid dysfunction

4. **Which one of the following statements is not correct:**
   a) Dental decay after HSCT may occur in patients with sicca syndrome, poor dental hygiene and large-scale consumption of sugar-containing drinks.
   b) Male patients surviving more than 10 years, younger than 25 years at HSCT, and apparently without chronic GvHD have a reasonable likelihood of spermatogenesis after HSCT.
   c) There exists a strong correlation between chronic kidney disease after HSCT and the use of prolonged corticosteroid therapy at increased doses for chronic GvHD.
   d) It is reasonable to treat patients with persistent high ferritin, over 2500 ng/L, or more than 7 mg/g dry weight liver iron for iron overload.

5. **One of the following post-transplant managements is not advisable in respect of late effects**
   a) Female patients conditioned with TBI should have regular mammography from the age of 30 years or from 8 years post-transplant.
b) All long-term survivors after HSCT should receive regularly bisphosphonates as a prevention of post-transplant osteoporosis.

c) To prevent therapy-related vascular late effects, patients should be encouraged to undertake regular physical activity, stop smoking tobacco, avoid passive smoking and maintain a healthy body weight.

d) For the treatment of cryptogenic organising pneumonia (COP) corticosteroids should be started without delay.