

## ORIGINAL ARTICLE

# Non-endocrine late complications in children after allogeneic haematopoietic SCT

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**Non-endocrine events represent a heterogeneous group of complications occurring in children who survive long term after haematopoietic SCT. This review highlights the late sequel in a growing child. The preparative regimen itself with high-dose chemotherapy and/or radiotherapy (TBI) or the treatment given before the transplant procedure may cause organ damage with permanent sequel. Immune reconstitution and chronic GvHD have crucial role in occurrence of clinical abnormalities and late severe infections. Autoimmune syndromes may occur after use of novel transplant modalities (cord blood transplantation, reduced intensity conditioning regimen and haploidentical T-cell-depleted SCTs). Exposure to chemo- and/or radiotherapy increases the risk of second malignant neoplasms. Surveillance strategy focusing on each potential complication risk at continuous follow-up will allow vigilant post transplant care. Each paediatrician must be well versed in appropriate monitoring of these complications. Guidelines and recommendations are provided for serious problems occurring at follow-up, which must rapidly be identified so that appropriate intervention can be initiated. To achieve cure at a lowest possible price in terms of suffering and cost expenditures for health care is an extended frontier of paediatric haematopoietic SCT and biggest challenge for a paediatrician.**

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### Introduction

Late complications occur after the first 100 days of transplant and timing of occurrence is slow. The problems occurring during the follow-up period are defined as any adverse event that does not resolve after completion of the

HSCT (haematopoietic SCT), or any new problem that becomes evident after completion the HSCT procedure itself. The primary aim of this report is the need for an optimal approach underlined to recognize the clinical manifestations of the late transplant complications to prevent, which can be avoided in at-risk patients. Screening for existing complications in addition is important for early discovery and appropriate intervention, which is essential for these complications. High-dose chemotherapy regimen with autologous stem cell rescue/support, called often for 'autologous BM or blood transplantation', apart from haematopoietic toxicity, equal or similar to all kind of cytostatic/radiological treatment. The autologous donor cells do not have any impact on the underlying disease or the recovery of the immune system. This manoeuvre, in fact, is not a transplant procedure and the frame of this review will not deal with autologous BM or blood transplantation.

The number of children surviving HSCT, performed both for malignant and non-malignant diseases, are considerably increasing. BM is the preferred stem cell source in children in contrary to dramatic switch to PBSCs in adults. The cohort of engrafted long-term paediatric survivors is rapidly growing not only due to substantial improvements in supportive care, but also due to increasing indications and optimized timing of the procedure itself, in combination with benefits of allele-level matching. The cohort of children who receive HLA-haploidentical T-cell-depleted stem cells is increasing as well, still facing a remaining risk for engraftment failure and infectious complications. Unsatisfactory results of conventional therapy for paediatric malignancies in addition gain further acceptance in a proportion of children for experimental procedures with cell therapy. Immune reconstitution in association with GvHD has a pivotal role in the long-term issue of complications. Apart from the life-long risk for recurrence of the underlying disease, non-relapse mortality due to second malignant neoplasms, long-term cognitive and psychosocial consequences have increasingly been documented.

Many of the special concerns of HSCT long-term survivors are highlighted in the studies performed by LEWP (Late Effect Working Party) of the EBMT

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(The European Group for Blood & Marrow Transplantation). Although guidelines for the follow-up of paediatric cancer survivors have been published by the Children's Oncology Group,<sup>1</sup> this cohort of HSCT children requires special recommendations.

### Immune reconstitution and vaccinations

The type and source of the graft substantially influence the recovery of immune function.<sup>2</sup> After BM graft, natural killer cells are the first ones to reconstitute (within 100 days), while the reduced B- and T-cell function gradually normalizes after 1 year. This process is much slower after use of UCB (umbilical/placental cord blood) stem cells, but improves progressively and is, in fact, at 2 years better than after BM-derived graft. After the infusion of PBSCs, the probability of GvHD occurrence is higher due to the high lymphocyte content (B and T cells) in the graft carrying an increased risk of infections. Presence or absence of GvHD, and the chronic one in particular, is the most important factor in immune reconstitution.<sup>3</sup> Type of conditioning regimen is an important variable. Use of reduced-intensity/non-myeloablative conditioning regimen always necessitates immunosuppression. Occurrence of autoantibodies may lead to clinical autoimmune syndromes. The number and function of B and T cells can also be influenced by the underlying disease, HLA difference and by type, duration and dosage of the immunosuppressive treatment, given to treat and/or to prevent GvHD (that is, ALG-anti lymphocyte globulin serum, ATG-anti thymocyte globulin serum, monoclonal antibodies, steroids, and so on). The low B-cells count secondary to immunosuppressive therapy (for example, use of anti-CD20-monoclonal antibody) can induce a low plasma level of immunoglobulin for a long time necessitating immune globulin supplementation.<sup>4,5</sup>

Immune reconstitution monitored by quantitative and qualitative assays (prior to HSCT, at engraftment, at days +100, +180 and +360) may identify the increased infection risk period and guide the preventive/pre-emptive therapy for viral infections.

Many patients over time following HSCT will lose immunity (levels of *in vitro* cell-mediated immune responsiveness) to a variety of vaccine-preventable bacterial and viral pathogens over a number of years, despite immune reconstitution. Falls in antibody levels have been documented for tetanus toxoid (TT), poliovirus; diphtheria; measles, mumps, rubella (MMR); and *Haemophilus influenzae* type b (Hib) fall in protective levels.

There are exceedingly few randomized controlled trials of immunization after HSCT; however, there is a good theoretical basis for its use, and responses to immunization are also generally good. Serious adverse events due to immunization have not been noted. Receiving more than one vaccine dose has been consistently associated with a better antibody response, supporting the theory that B-cell immunity derives largely from donor stem cells rather than memory cells.

The recommendation of EBMT<sup>6</sup> for all patients is to receive tetanus toxoid, diphtheria toxoid, inactivated poliovirus, pneumococcal, *H. influenzae* and influenza

vaccines. There have been no differences in terms of response rate for tetanus and polio vaccines noted between those with and without GvHD, although those without GvHD tend to have higher antibody levels. Measles and rubella immunization is considered an individual recommendation based on risk and benefit assessment with vaccination not to be given before 24 months in allogeneic recipients. Conjugated tetravalent meningococcal type A and C vaccines are available and recommended if indicated; hepatitis B vaccine is recommended as per routine use, while MMR, varicella and yellow fever vaccines may be considered at 24 months if there is no immunosuppressive therapy or underlying disease. CAVE: oral polio, typhoid and cholera vaccines, as well as Bacille Calmette-Guerin are, however, contraindicated. Improving the response of patients to immunization after HSCT is clearly a goal for these patients.

### Chronic GvHD and organ involvement

In spite of lower incidence in children, cGvHD (chronic GvHD) represents a main cause of mortality.<sup>7</sup> Only 22–29% of paediatric recipients develop cGvHD in comparison with adults' 30–50%, being usually less severe, and the cumulative probability of developing limited or extensive cGvHD is 17 and 11%, respectively.<sup>7</sup> Zecca *et al.*<sup>7</sup> identified older age of recipient and donor, female donor, malignant disease, TBI (total body irradiation) and previous aGvHD (acute GvHD) > II grade as the risk factors in paediatric patients.

No specific laboratory tests are available to detect, monitor or follow up cGvHD. Haematologic abnormalities such as auto- and alloimmune haemolytic anaemia are recognized complications of HSCT occurring with increasing frequency in patients receiving an URD (unrelated/voluntary HLA matched donor) transplant and in those undergoing transplantation for non-malignant diseases. Definitive diagnosis of cGvHD is possible with histopathologic examination of the biopsy material, along with clinical correlation. However, some patients may have serum evidence of autoimmunity or altered cytokine production.

The current definitions of cGvHD are based on the subjective assessment.<sup>8</sup> The National Institutes of Health, in June 2005, sponsored a consensus on standardized criteria for the diagnosis and follow-up of cGvHD.<sup>9</sup> A clinical score between 0 and 3 was proposed for all organs/sites affected by cGvHD: i.e., skin, mouth, eyes, gastrointestinal tract, liver, lung, joints, fascia and genital tract (Table 1).

New categories of GvHD have been defined.<sup>9</sup> Two subgroups were proposed for aGvHD:

- I Classic aGvHD (occurring within 100 days of HSCT)
- II Persistent, recurrent or late aGvHD occurring > 100 days after transplant.

The category of cGvHD was subclassified into two groups:

- Classic cGvHD

**Table 1** Organ severity scoring in chronic GvHD

0	1	2	3
Absence of cGvHD	No impairment of function or activities of daily living	Significant impairment of activities of daily living but no disability	Significant impairment of activities of daily living with major disability

- Acute and chronic overlap GvHD syndrome in which features of both acute and chronic GvHD appear together.

Skin is the most common organ affected by cGvHD (83%)<sup>9</sup> and cutaneous manifestations of cGvHD include erythematous rash, sclerosis (movable or not), itching and ulcers. Skin fibrosis is a debilitating disease resembling idiopathic scleroderma characterized by excessive dermal fibrosis with later progression to internal organs. In addition to the fibrotic component, major aspects of the disease include vascular or circulatory involvement. Affected skin samples showed markedly decreased numbers of Langerhans cells, deposition of lymphocytes and Ig-complexes. Immune dysregulation is evidenced by deposition of excess collagen and inflammatory cells in affected tissues. Production of autoantibodies is often compatible with an immune aetiology with joint involvement and/or fascial thickening.

For cGvHD-associated organ dysfunction and manifestations refer to subsequent chapters on respective organ abnormalities. The haematopoietic system itself may be affected by anaemia, thrombocytopenia and eosinophilia. Unfortunately, with the increased use of reduced-intensity/non-myeloablative conditioning regimen, including monoclonal antibodies (such as Campath), a number of autoimmune phenomena<sup>10</sup> have occurred. Patients with cGvHD are at increased risk for opportunistic infections, especially those receiving immunosuppressive therapy and with CD4<sup>+</sup> count <0.2 × 10<sup>9</sup>/l, for example, PCP (*Pneumocystis pneumonia Jiroveci* (carinii) or *Toxoplasma gondii* infection. Trimethoprim-sulphamethoxazole prophylaxis is recommended to continue for several weeks after cessation of immunosuppressive therapy.

Optimal care of patient with cGvHD often requires a multidisciplinary approach. Many clinical trials have focused on the prevention of GvHD and multiple strategies have shown varying degree of success. These include different selectivity and different ways to manipulate the graft product. Many trials have demonstrated success at reducing GvHD, but with increased risk of late graft failure and relapse, particularly relevant for those diseases for which alloreactivity has a role in disease control. Corticosteroids are the first line of treatment for patients with severe aGvHD, however, no optimal choice of alternatives is available for GvHD unresponsive to corticosteroid therapy. Clinical trials to guide prevention strategies and treatment of cGvHD in the late post transplant period are still needed, in spite of broad experience with steroids used in association with calcineurin inhibitors (cyclosporine-A-CSA, tacrolimus, sirolimus, everolimus), ATG,

rapamycin, azathioprine, MMF (mycophenolate mofetil), humanized monoclonal antibodies against signal transduction receptors, for example, daclizumab, infliximab, psoralen with exposure to ultraviolet light A, extracorporeal photopheresis and others.<sup>11</sup> The last two are considered effective for curing cutaneous cGvHD.<sup>12</sup> The use of cold cream is recommended to prevent cutaneous ulcerations, while suntan lotion prevents activation of skin cGvHD. Range-of-motion exercise is important to prevent contractures.

### Late onset non-infectious pulmonary complications

Pulmonary complications are less frequent causes of morbidity and mortality in paediatric graft recipients,<sup>13,14</sup> still being one of the most challenging problems facing clinicians who are taking care of HSCT children. Cerveri *et al.*<sup>15</sup> reported one third of surviving children after HSCT having sub-clinical lung function abnormalities, while Uderzo *et al.*<sup>16</sup> reported 35% cumulative incidence of lung failure at 5 year. Pulmonary function testing (PFT) is the most reliable method for detection and follow-up of LONIPC (late onset non-infectious pulmonary complication) occurring >100 days after HSCT.<sup>17</sup> Based on PFT, the LONIPC can be divided into two major groups.<sup>17,18</sup>

- Obstructive respiratory insufficiency is characterized by reduction in forced expiratory volume in 1 s (FEV1), while forced vital capacity (FVC ≥ 80%) remains normal, resulting in decrease of the FEV1/FVC ratio (<70%).<sup>19</sup> This functional constellation is the result of obstruction in the small airways caused by donor T cells' direct immune-mediated damage (that is, cGvHD) or of indirect cGvHD (that is, aspiration secondary to oesophageal cGvHD, abnormal mucociliary transport).<sup>3</sup>
- Restrictive respiratory syndrome shows decreased FVC (<80%) and the FEV1/FVC ratio is ≥70%.

Table 2 summarizes the characteristics of the classification of LONIPC proposed by Anfessa *et al.*,<sup>20</sup> which includes bronchiolitis obliterans syndrome, bronchiolitis obliterans organizing pneumonia and idiopathic pneumonia syndrome.

Bronchiolitis obliterans syndrome may be debilitating and should be discovered early by serial routine spirometry, available for an age-dependant cooperative child. Symptoms are persistent cough, wheezing and recurrent respiratory tract infections. Chest radiography and high-resolution chest computerized tomography may reveal patchy infiltrates, although a definitive diagnosis is established by means of bronchoscopy with transbronchial biopsy, which preferably should be performed. Bronchoalveolar lavage should exclude infectious causes. Severe airway obstruction or thrombocytopenia,<sup>20</sup> however, might contraindicate invasive approach.

Interstitial pneumonitis occurs in 20–50% of patients after allogeneic HSCT and in 10% of patients treated with autologous HSCT. It generally occurs in the first 4 months after HSCT, but it can occur later than this. The mechanism of non-infectious pulmonary abnormalities

**Table 2** Characteristics of LONIPC

LONIPC	Incidence %	Onset months	Clinical findings	Risk factors	Diagnosis	Mortality %	Therapy
BOS	3–4.5	3–23	Cough, dyspnoea, wheezing	cGvHD, MTX, ↓ gamma globulin level, oesophagitis	↓ FEV1, CT = air trapping/ bronchiectasis/ bronchial dilatation	14–100	Steroids MMF AZA CSA aerosol lung transplant
BOOP	1.4	1–13	Cough, fever, dyspnoea	cGvHD	↓ FVC, ↓ DLCO, CT = peripheral consolidations/ ground-glass/ nodular opacity	21	Steroids
IPS	2–20	0–48	Dyspnoea, dry cough, hypoxemia	Damage by chemo and/or radiotherapy TBI/cGvHD/ infection	X-ray = infiltrates	74	Steroids

Abbreviations: AZA = azathioprine; BOOP = bronchiolitis obliterans organizing pneumonia; BOS = bronchiolitis obliterans syndrome; Chemo = chemotherapy; CT = computerized tomography; DLCO = diffusing capacity for carbon monoxide; FEV1 = one second forced expiratory volume; FVC = forced vital capacity; IPS = idiopathic pneumonia syndrome; LONIPC = late onset non-infectious pulmonary complication; MMF = mycophenolate mofetil; MTX = methotrexate.

appears to be immunologic, similar to GvHD, as manifested by the increased severity of these changes when transplants are obtained from allogeneic donors. Abnormal PFT results with a restrictive pattern were observed 3–6 months after HSCT, especially after preparative regimen including TBI. In a retrospective study<sup>21</sup> of children monitored for a prolonged time (> 10 years) and receiving TBI, PFT abnormalities were reported in 74% of patients at 3 years after TBI. PFT improved in 37% in mild restrictive disease after a median of 4.2 years, whereas remained stable with no significant worsening in the rest. Obstructive lung disease can be detected in as many as 20% of survivors after HSCT, and they are frequently associated with IgG and IgA deficiency, chronic GvHD, infections, use of methotrexate and TBI. Pulmonary complications also correspond to the total radiation dose given during conditioning, the dose rate and the dose fractionation scheme.

Pulmonary function testing, as screening for pulmonary abnormalities, is strongly recommended by the EBMT/CIBMTR/ASBMT guidelines<sup>5</sup> and should be performed in cooperative children every 3–6 months in the first 2 years, in particular in patients with cGvHD and yearly during long-time follow-up. Patients with Ig deficiency should be given i.v. supplementation and asymptomatic patients with abnormal PFT results should be closely monitored for development of overt pulmonary disease. No tobacco smoking, protection from pollution and prevention of common respiratory infections (vaccinations) are recommended in addition.

### Cardiac function abnormalities

The clinical manifestations of cardiac damage include congestive cardiac failure, arrhythmias, fatal cardiomyo-

pathy, pericardial and valvular disease, electrocardiogram abnormalities or asymptomatic reduction of left ventricular fraction shortening (SF < 30%) on echocardiography. The ejection fraction measures the left ventricular performance, while the SF is a slightly different way of measuring ratios of the change in the diameter of the left ventricle between the contracted and relaxed states. Cardiac involvement is distinctly uncommon, although findings consistent with cGvHD have been identified in the myocardium of some patients. Heart attack, an exceedingly uncommon event has been reported to be a potential manifestation of myocardial GvHD. Complete heart block in an infant is also reported, presumably secondary to cGvHD.

The long-term cardiotoxicity major risks are related to treatment before HSCT, particularly anthracycline therapy at doses > 250–300 mg/m<sup>2</sup>, myeloablative doses of cyclophosphamide > 150 mg/kg, iron overload and chest radiation therapy. Almost all preparative regimens contain myeloablative doses of cyclophosphamide with a potential to cause haemorrhagic myocarditis, especially in patients with pre-existing cardiac injury. Radiation therapy further enhances this toxicity, as high-dose steroids and TBI (especially without fractionation) remain the only risk factor for cardiac abnormalities.<sup>16,17</sup> Uderzo *et al.*<sup>16</sup> reported 23% cumulative incidence of SF abnormalities in a multi-centre study of 189 paediatric allogeneic recipients 5 years after HSCT, but none of the patients died of cardiac-related complications. Liesner *et al.*<sup>22</sup> reported 3.5% significant cardiomyopathy in 83 children, evaluated 3 years after TBI. Most patients have some cardiac dysfunction during and immediately after HSCT and as many as 50% have persistent abnormalities, usually subclinical and rarely limiting the quality of life.

Late onset of congestive heart failure has been reported after HSCT performed in childhood, during pregnancy, rapid growth and, in addition, following initiation of

vigorous exercise programmes in adults or young adulthood. This may occur as a result of increased afterload and the effect of the additional stress of such events on marginal cardiac reserves or diminished compensatory mechanisms in the presence of stressors or myocardial depressants such as alcohol. Cardiotoxicity increases over time, even without further therapy for the underlying disease for which transplantation was performed. Children who survived HSCT for <3 years had fewer abnormalities than those who had survived for >3 years, even when they were treated with similar preparative regimens. One is prone to speculate that discrepancy over time is related to loss of reserve of heart muscle, early progression of atherosclerosis or even chronic GvHD.

Hormonal deficiencies may predispose to heart disease. Almost all post pubertal women and one-half of prepubertal girls develop oestrogen deficiency and loss of normal protective effect of oestrogen against coronary artery disease.<sup>23</sup> Metabolic syndrome including systemic hypertension can also cause cardiomyopathy.<sup>24</sup> All these findings suggest that damaging effects may be related to cumulative chemotherapy and radiation toxicity rather than to the transplant procedure itself.

Anthracycline-induced cardiotoxicity is suggested to be reduced with a concurrent use of dexrazoxane. Amifostine may have cardioprotective effect too.

Cardiac screening is recommended prior to HSCT and yearly afterwards. The echocardiogram (ECHO) is the 'work horse' test for anthracycline-induced cardiomyopathy, as cardiac dysfunction may not be evident with conventional testing at rest. Significant cardiotoxicity can be detected during exercise stress echo. To acquire information regarding size, volume, ventricular systolic function, cardiac mass and function, especially in patients with risk factors for cardiac toxicity, evaluation is routinely obtained by two-dimensional directed M-Mode echo. HSCT performed in childhood often qualifies asymptomatic long-term survivors to get monitored continuously, especially during adolescence and pregnancy. Young adults need more sophisticated follow-up and evaluation of the cardiopulmonary exercise performance.<sup>16</sup> Multiple uptake gated acquisition is another way of estimating the ejection fraction. A radioactive tracer is injected into the blood stream and then the heart is viewed using a gamma camera, resulting in a 'movie' of the heart beating from which various measurements can be made. In general, it is more precise than an echo, but it is also more expensive and somewhat limited in accessibility.

### Eye abnormalities

The most common ocular complications include ocular sicca syndrome, early cataract development and ischaemic microvascular retinopathy.<sup>5</sup> Dry-eye syndrome can be a sign of cGvHD and corneal microscopy will detect lymphocytic deposition. Schirmer's test is used for routine evaluation of cGvHD involvement of the eye and does determine whether the eye produces enough tears to keep it moist.

Visual defects are common in children surviving >5 years after HSCT, developing almost one-third long-term

visual defects. The common defect is premature cataract or sub-capsular posterior opacity development secondary to irradiation and/or steroid treatment. The expected cataract development is later, and the incidence somewhat lower when the TBI technique used was hyperfractionated.<sup>25,26</sup> Tichelli *et al.*<sup>27</sup> reported an increase from 29 to 83% premature cataract in adults 4 and 6 years after single fraction TBI. In a paediatric cohort surviving more than 10 years after fTBI an incidence of 78% cataracts was observed at median interval of 5.7 years after transplant.<sup>21</sup> Long-term steroid treatment accelerated cataract occurrence, as does cGvHD.<sup>26</sup>

Retinopathy after HSCT can be associated with combination of TBI/busulphan or CSA. The fundus view is characterized by cotton-wool spots and optic oedema can be treated by reducing or discontinuing immunosuppressive therapy. Retinal microvascular incompetence, however, with good vision may also be detected as a late complication in a small number of patients.<sup>28</sup>

Infrequent eye complications include retinal haemorrhages and panuveitis. Early after HSCT, cortical blindness and microvascular retinopathy are two main causes of deteriorating vision. CSA has been implicated in the pathogenesis. Exclusion of organic brain disease, meningitis and encephalitis supplemented by magnetic resonance imaging and funduscopic examinations are usually sufficient for diagnosis. In patients with continuously deteriorating vision, electroretinography and visually evoked cortical potentials can be useful in diagnosing retinal damage.

A routine ophthalmologic control, including evaluation of visual acuity and fundus examination, is recommended before HSCT and yearly thereafter. Artificial tears may alleviate sicca syndrome in children affected by ocular dryness, suffering from photophobia, irritation and ocular burning. Cataract surgery and implantation of accommodating intraocular lenses is the treatment of choice.

### Oral and dental complications

Oral mucositis is a common complication after HSCT. Keratinocyte growth factor has been used to prevent conditioning-related mucositis in adults pretreated with palifermin, but studies in children are warranted. Young age at time of HSCT is a risk factor for a substantial rate of dental abnormalities, including serious gingivitis, periodontal involvement, dentofacial abnormalities, tooth agenesis and dental root hypoplasia. In cGvHD of the mouth mucosal erythema, lichen-type hyperkeratosis, ulcerations and xerostomia may lead to dental complications. Microdontia, hypoplasia and arrest of the root development are the most common findings.<sup>26</sup> The prolonged reduction of salivary gland secretion occurring especially after TBI<sup>29</sup> has been suggested as a possible reason for dental complications. Decreased salivary secretion resolved within 4 years in most patients who received conditioning with chemotherapy as preparation, but it persisted in all who received TBI. This finding suggests that the damage to salivary glands may be permanent after radiation.

Maintaining sufficient active oral hygiene and treating xerostomia may prevent development of serious caries.

Dental evaluation yearly and careful continuous oral hygiene should be offered all allogeneic recipients.<sup>5</sup>

### Renal complications

Most children have normal renal function years after treatment, but 11% may remain asymptomatic still having on testing haemofiltration abnormalities or hyposthenuria. Kist-van Holthe and co-workers reported chronic renal insufficiency correlated with a high serum creatinine level that occurred within the first 3 months of HSCT.<sup>30</sup> The incidence of late HSCT nephropathy in children ranges from 17<sup>31</sup> to 28%<sup>30</sup> with onset within a year of transplant. Late nephropathy with rapid deterioration of renal function can present acutely in association with haemolytic anaemia, while chronic onset may occur after gradual decline in kidney function.<sup>32</sup> Irradiation and in particular TBI in combination with immunosuppressive and supportive medication represent the main risk factors for patients who developed chronic renal impairment.<sup>33</sup> Miralbell *et al.*<sup>34</sup> reported renal dysfunction after allogeneic HSCT strongly related to TBI dose and GvHD. They suggest shielding of the kidneys in patients at high risk of developing GvHD who receive TBI doses greater than 12 Gy. Late-onset haemorrhagic cystitis is sometimes associated with BK/JC, adeno- and/or polyoma viruses, although a cause-effect relationship has not been proven. Cidofovir and vidarabine have been used to successfully treat viral associated haemorrhagic cystitis.

According to good clinical practice, yearly monitoring of the blood pressure, creatinine, BUN, glomerular filtration rate estimate with some clearance test and urinary cast analysis should be performed in patients who received TBI and/or nephrotoxic drugs before and after HSCT.

### Gastrointestinal and liver complications

Gastrointestinal and liver cGvHD in paediatric recipients are 24 and 28%, respectively.<sup>9</sup> Dysphagia, pain, weight loss are the most common manifestations and increased levels of conjugated bilirubin, elevated transaminases and gamma glutamic-transpeptidase the usual findings.

Hepatitis, cGvHD and iron overload can be the cause of late liver dysfunction.<sup>5</sup> Clinical assessment, transplant history (that is, occurrence of veno-occlusive disease/sinusoid occlusion syndrome or viral infection) and whenever possible, performing a liver biopsy is the diagnostic approach to transplanted patients with late liver problem. Viral hepatitis B and C patients are often asymptomatic, but they run a risk of developing cirrhosis.<sup>3,35</sup> Long-term follow-up should be carefully performed to discover advanced liver disease. Liver siderosis was the most common histological finding in patients with liver dysfunction who underwent liver biopsy.<sup>36</sup> Hepatic iron overload can be the consequence of chronic hepatitis, opportunistic infections and multiple transfusions.<sup>3</sup>

In children with gut and hepatic cGvHD, use of total parenteral nutrition to supply an adequate caloric intake,

as well as ursodeoxycholic acid can improve the quality of life. After haematopoietic reconstitution, children with iron overload may undergo phlebotomies alone or associated with iron chelation<sup>37</sup> monitored by ferritin levels and cardiac function<sup>5</sup> by means of magnetic resonance imaging-based relaxation parameters T2 and T2\*.

### Complications affecting the locomotor apparatus

The main late complication affecting bones include avascular necrosis (AVN) and osteoporosis.<sup>26</sup> Magnetic resonance imaging with an overall sensitivity of more than 90%<sup>38</sup> is the most sensitive method for diagnostic detection and follow-ups of AVN. The disease results from the temporary or permanent loss of the blood supply to the bones. Such ischaemic damage induces reduction or obliteration of the blood flow, which results in bone infarction and anoxic death of haematopoietic, osteoid and marrow fat cells. The osteoid does not mineralize properly and the bone tissue dies. If the process involves the bones near a joint, it often leads to collapse of the joint surface and arthritis. Although it can happen in any bone, AVN usually affects the ends of long bones such as the femur, the hips—being the most common localization—resembling Legg-Calvé-Perthes syndrome, but small bones of the hands and/or feet may also be affected. Other common sites include the upper arm bone, knees, shoulders, ankles and the jaw. AVN may affect just one bone, more than one bone at the same time or more than one bone at different times. Until the necrotic process involves the medulla of the bone, AVN remains asymptomatic. Onset of clinical symptoms starts once necrosis occurs in the cortical area. AVN may lead to significant morbidity and compromised quality of life with an incidence ranging from 4.3<sup>39</sup> to 19%.<sup>40</sup> Older age at transplant, acute and chronic GvHD, underlying disease and TBI are the main risk factors.<sup>39–42</sup> In a recent Italian case-control paediatric study, the risk factors associated with AVN in a multivariate analysis were older age at HSCT, TBI and cGvHD.<sup>43</sup> Continuous and longer use of steroids after HSCT was, however, not associated with the risk of developing AVN, nor the cumulative doses used.

Pain relief (pharmacological or surgical measures, such as core decompression) is the goal of recommended treatment. In an early phase of AVN, patients should use crutches or other supports to avoid weight load on the limbs, whereas in advanced disease, surgery remains the only option. Since AVN can be considered a disease of the mesenchymal cells, replacing mesenchymal cells containing osteogenic precursors into the necrotic lesion might be beneficial.<sup>44</sup>

Osteopenia and osteoporosis are common complications after HSCT. Bone density scanning, also called dual-energy X-ray absorptiometry (DXA or DEXA) or bone densitometry, is an enhanced form of X-ray technology that is used to measure bone loss. DEXA is the established standard for measuring bone mineral density in adults.<sup>45</sup> In children, however, osteopenia/osteoporosis is a more complex problem. DEXA reference values do not exist for the paediatric cohort of patients. Hypogonadism (low

oestrogen and testosterone level) appear as the main risk factor in transplanted children and prolonged steroid medication given before and after HSCT.<sup>26,46</sup> To alleviate the clinical manifestations (pain, fractures and so on),<sup>5</sup> vitamin D and calcium supplementation, hormone replacement therapy and bisphosphonates are in use.

## Second malignant neoplasms

Increased risk of second malignant neoplasm has been documented up to 20 years after transplantation in childhood.<sup>47</sup> Skin and oropharyngeal cancers predominate and solid tumours as do thyroid and breast cancer. Being at risk after radiation therapy alone, chemotherapy alone and combined chemo- and radiotherapy, these risks apply to patients who undergo HSCT at a younger age,<sup>48</sup> although a genetic predisposition may have a role in the development of second malignant neoplasms.<sup>49</sup> Sociè *et al.*<sup>50</sup> reported higher risk of occurrence of solid tumours in paediatric patients transplanted below the age of 5 years. Cancer of the brain and thyroid did represent half of all secondary tumours occurring most frequently in very young transplanted patients. Whether the risk is higher in these patients than in patients undergoing standard high-dose chemo- and/or radiotherapy has not yet been well defined. Risk factors include previous radiotherapy, TBI and/or chemotherapy (especially alkylating agents), cGvHD (oropharyngeal cancer and skin).<sup>5</sup>

Secondary lymphoproliferative diseases and haematological malignancies include myelodysplastic syndrome, acute myeloid leukaemia and post-transplant lymphoproliferative disorder (PTLD). Myelodysplastic syndrome and acute myeloid leukaemia are classically correlated with the cancerogenic effect of chemotherapy.<sup>26</sup> The type associated with the Epstein–Barr virus (EBV), is called B-cell (monoclonal, oligoclonal or polyclonal) lymphoproliferative disease (EBV-LPD) and may be fatal. Baker *et al.*<sup>49</sup> reported, in a paediatric population, 1.4% incidence of PTLD 20 years after HSCT and risk factors include type of graft (mismatched related donor), primary immunodeficiency, use of ATG, T-cell depletion and aGvHD>II grade. ATG is associated with increased depletion of T lymphocytes, including those active against EBV-infected cells. T-lymphocyte dysfunction after transplant secondary

to immunosuppression, allows the EBV-infected B lymphocytes to proliferate in uncontrolled fashion. This proliferation occurs with the highest frequency in patients who receive T cell-depleted haematopoietic donor cells. Patients with the monoclonal form have survival rates poorer than those of patients with the polyclonal form. Polyclonal EBV lymphoproliferative disorder may resolve with a suspension or decrease of immunosuppression with or without systemic use of immunoglobulins, acyclovir or interferon. Monoclonal disease, however, usually does not respond to such simple measures and chemotherapy with or without radiation therapy may be required. Prophylactic use and treatment benefit of monoclonal antibody that targets B-cell antigens, such as rituximab (anti-CD20), can also be effective. T-cell LPD is rare with only a few cases reported.

Long-term follow-up for second malignant neoplasms, as part of good clinical praxis, is strongly recommended in patients who received HSCT in the paediatric age (see Table 3).<sup>49</sup>

## Neurological late complications and cognitive/psychosocial consequences

Irradiation delivered to the central nervous system and neurotoxic agents is used in conjunction or before HSCT produce permanent neurological and cognitive sequel, especially in very young children.<sup>5,18</sup> In a prospective longitudinal study, Phipps *et al.*<sup>51</sup> found less neurocognitive sequelae in children who underwent HSCT at an older age, but performed below the age of 3 years carried an increased risk of cognitive defects. Front line treatment of the underlying disease with radio- and/or intrathecal chemotherapy given before HSCT may cause progressive damage of the central nervous system and mental deterioration, leading to neuropsychological symptomatology.<sup>18,49</sup> Patients affected by predisposing conditions (neurotoxic treatment given in first-line therapy, CSA neurotoxicity, anoxic injury) may develop mesial temporal sclerosis with clinical finding of temporal intractable epilepsy.<sup>52</sup> Leukoencephalopathy, mineralizing microangiopathy, necrotizing leukoencephalopathy and brain atrophy<sup>5,18,53</sup> are diagnosed by magnetic resonance imaging of the brain.

**Table 3** Risk factors and screening recommendations for second malignant neoplasms

Risk factors	SMNs	Screening recommendations
Etoposide, teniposide, anthracyclines, alkylating drugs	AML, AML/MDS	Complete blood count, platelet, differential yearly for 10 years after exposure
Radiation therapy	SMN in radiation field: skin, bone, soft tissues	Annual history and physical check up
Radiation therapy affection thyroid (TBI)	Thyroid cancer	Yearly US examination
Radiation therapy affection breast (TBI)	Breast cancer	Physical examination until age 25, then mammography and US yearly starting 8 years after irradiation

Abbreviations: AML = acute myeloid leukaemia; MDS = myelodysplastic syndrome; SMN = second malignant neoplasm; US = ultrasonography.

Hearing abnormalities and incidence of ototoxicity are increased in patients who are treated with cyclophosphamide, thiopeta, cisplatin and carboplatin either as a part of the chemotherapy or the conditioning regimen before HSCT.

Children treated with HSCT during infancy should thus be carefully monitored for a very long time.

### Health-related quality of life

Evaluation of health-related quality of life in children is an extending frontier. In a large cohort of paediatric patients type of graft (unrelated vs related and autologous), older age and lower socioeconomic status<sup>51</sup> were identified as predictive factors of distress related to health-related quality of life. Recently, Felder Puig *et al.*<sup>54</sup> carried out a longitudinal prospective study on health-related quality of life in paediatric recipients using Pediatric Quality of Life Inventor and Health Utilities Index Mark 2 + 3 (HUI2/3). They concluded that the majority of children have good health-related quality of life 1 year after HSCT. Among the young adult population who received HSCT during childhood, a high level of sensitivity, vulnerability and anxiety was observed,<sup>55</sup> indicating a risk of developing long-term emotional or social problems.

Children after HSCT as curative procedure face many risks on the way to achieving adulthood. All the described problems *per se* and in combination do potentially increase the risks of long-term cognitive and psychosocial consequences. Continuous follow-up must assess organ function, focus on vaccinations, screening for secondary malignancies and cognitive–psychosocial disorders. Knowledge provided on the potential risks and complications will result in optimal surveillance strategies. Adequate care means identifying the need and proper timing for the initiation of certain action.

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### Conflict of interest

None of the authors declared any financial interests.

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