15 Late Effects and Long-Term Follow-Up

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Abstract

Allogeneic stem cell transplantation was successfully performed in 1968, and its use has grown significantly over the past five decades with the total number now exceeding 1.5 million patients (Niederwieser et al. Haematologica. 107:1045–1053, 2022). HSCT is a curative treatment for many haematological cancers and other disorders. Almost 40,000 HSCT procedures are performed Europe-wide per annum (Passweg et al. Bone Marrow Transplant. 51(6):786–92, 2016), and the number of transplant recipients achieving 'long-term survival' and with late effects directly related to their treatment (Majhail et al. Hematol Oncol Stem Cell Ther 5(1):1–30, 2012) is increasing (Penack et al. Blood Adv 4:6283–6290, 2020). This growth in survivors is the result of improvements in transplant knowledge and expertise, refinements to conditioning regimes, developments in supportive care and increased numbers of procedures due to broadening transplant indications.

The most common cause of death after transplant is relapsed disease. Yet, even without disease relapse, long-term survival is complex for many as other causes of mortality such as graft versus host disease (GvHD), infection, second malignancy, respiratory disease and cardiovascular disease (CVD) (Savani et al. Blood. 117:3002–9, 2011) prove difficult to address.

Recovery post-HSCT is challenging, lasting several months to years. These individuals are susceptible to the development of post-treatment physical and psychological sequelae years to decades after completion of treatment leading to a reduced life expectancy with greater morbidity when compared to an age-adjusted population (Socié et al. N Engl J Med 341:14–21, 1999). Survivors with late effects experience significantly poorer physical and mental health, report more unmet needs for

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care and have significantly greater use of health services compared with survivors without late effects (Treanor et al. Psychooncology 22(11):2428–2435, 2013).

Furthermore, as the number of survivors continues to grow, their long-term health problems and subsequent needs demand increasing resource and attention from late effects services. These services must remain agile and responsive, develop capacity to provide continuing expertise and oversight and collaborate with the other specialist services for input when needed.

The unpredictable, complex and multifactorial nature of these long-term and late effects in HSCT survivors means that patients require regular life-long assessment guided by rigorous protocols. However, it is important to remember that even using standardised protocols, these should be different for adults and children and the resulting care must be tailored to the needs of the individual. And finally, further consideration is needed for the growing number of young people and adult survivors in long-term follow-up who have been treated in childhood and transitioned into adult long-term follow-up care.

Keywords

Late effects · Survivorship · Survivors · Follow-up

15.1 Principles of Care

Protocol-led assessment and treatment is included in the current FACT-JACIE standards (version 8, 2021), which has evolved the standard of care recommending the assessment of recipients for evidence of acute and chronic GVHD, need for vaccinations and post-transplant late effects.

B7.12 54 There shall be an infrastructure and policies or standard operating procedures in place for provision of appropriate long-term follow-up, treatment and plans of care.

B7.12.1 There should be policies or standard operating procedures in place for post-transplant vaccination schedules and indications.

B7.12.2 There shall be policies and standard operating procedures for monitoring by appropriate specialists of recipients for post-cellular therapy late effects, including at a minimum:

B7.12.2.1 Endocrine and reproductive function and osteoporosis

B7.12.2.2 Cardiovascular risk factors

B7.12.2.3 Respiratory function

B7.12.2.4 Chronic renal impairment

B7.12.2.5 Secondary malignancies

B7.12.2.6 Growth and development of paediatric patients.

B7.12.3 There shall be policies or standard operating procedures describing the transition of long-term paediatric recipients to adult care as appropriate.

A further benefit of life-long survivorship care is the acquisition of knowledge and understanding through data collection and analysis which in turn facilitates the design and delivery of appropriate services that will better meet the needs of future survivors.

Late effect: A health problem that occurs months or years after a disease is diagnosed or after treatment has been administered. Late effects may be caused by the primary disease or its treatment and may include physical, mental or social problems and/or secondary cancers (ISCT, FACT-JACIE standards 2021).

15.2 Survivorship and Quality of Life

While there are many definitions of survivorship, it is widely accepted that a survivor is anyone living after a diagnosis of cancer or 'living with and beyond cancer'.

Survivorship includes 'those who are undergoing primary treatment, those who are in remission following treatment, those who are cured and those with active or advanced disease' (DoH 2010).

By developing and implementing strategies to improve the care and support for HSCT survi-

vors, we will also improve their quality of life and experience of care.

There are a broad range of issues experienced by HSCT survivors which are detrimental to overall quality of life (QoL) and have been reported in the literature.

Unmet physical or psychological needs are reported in 60% of cancer survivors. Beyond the first post-HSCT year, a fifth report psychosocial difficulties including fatigue, social reintegration, finance and employment. A third worry about the future and their health (Baker et al. 1999; Andrykowski et al. 2005; Gielissen et al. 2006).

Finance, employment and education are leading survivor concerns. The economic cost of cancer is a substantial personal and societal problem; 92% of sufferers lose income, impacting adversely on QoL for 40% (Bieri et al. 2008). These are among the major challenges that significantly hinder the cancer patient survivorship transition from treatment phase to reintegration phase and limit the post-HSCT potential for personal growth and fulfilment. A more recent study (Hahn et al. 2017) using Survivor Unmet Needs Survey (SUNS) in HSCT recipients attending a long-term follow-up clinic between 2006 and 2012 supports the finding from these earlier works. The top 5 specific unmet needs for autologous HSCT patients were inability to set future goals/long-term plans, changes in appearance, bad memory/lacking focus, losing confidence in abilities, and paying household or other bills. For allogeneic HSCT patients these 5 unmet needs were: ability to earn money, pay bills, feeling tired, feeling depressed and dealing with others' expectations of 'returning to normal'.

Work and education are immensely important to cancer survivors (Snyder et al. 2002) and have health benefits, and interventions addressing return to work are cost-effective (Waddell and Burton 2006). Reintegrated survivors are more likely to self-manage (Richards et al. 2013), make a positive contribution to self and society, depend less on the state financially and potentially reduce healthcare costs.

A range of psychological and psychosocial interventions including education, exercise, counselling, cognitive behavioural therapy (CBT) and psychotherapy have been investigated, aiming to address survivor concerns and improve overall quality of life.

15.2.1 Quality of Life Assessment

There is a new emphasis on understanding and monitoring the concerns and outcomes for cancer survivors through the routine use of patient-reported outcome measures (PROMs) in follow-up services. Quality of life (QoL) is an important outcome measure following HSCT. Treatment-specific QoL tools exist and have been validated in patients receiving haematopoietic stem cell transplant.

Instruments for assessing QoL can be general or specific to a certain disease or treatment. A number of cancer-specific tools (QLQ-LEU, EORTC SF 36, FACT-G/ FACT-BMT) exist and can be seen in publications of large-scale studies. They are often holistic, assessing different dimensions of well-being, such as physical, emotional, social/family and functional. Many of the commonly used scales such as EORTC and FACT are self-complete and produce a numeric score from which an inference on the relative QoL can be drawn.

These holistic assessments can be used to collect information on individuals at set time points during treatment and recovery and also can increase our knowledge of our patients as a group or groups. QoL data can help us to understand the differences between groups, e.g. comparing QoL in male versus female recipients or haploidentical versus cord recipients.

Standardised assessment tools can reveal information in certain groups or individuals that may not have been previously identified through conventional outpatient consultation alone. This can lead to increases in referrals to other services such as counselling, assisted conception, sexual dysfunction, social work, etc.

At a local level, this increase in referrals can have resource implications, but it can also lead to:

- Formalising referral pathways.
- Cultivating interest and expertise in certain areas.
- Developing services that meet the unmet holistic needs of patients.

Furthermore, this information can be used to:

- Identify how quality of life can be improved for individuals and to help plan care for individual patients.
- Assess patient experience and quality of care in individual services.
- Measure progress on survivorship care across networks or countries.

This holistic approach to assessment can be validated for patients while identifying individual information and supportive care needs. These needs can be met through a discussion with a healthcare professional, which is supported by written or multimedia materials and offers signposting for individuals to high-quality information and support (Table 15.1). The table below illustrates the most common issues expressed through assessment. They are multidimensional in nature representing psychological, physical and functional concerns.

Table 15.1 Top 10 common concerns (www.eHNA/Macmillan.org.uk analysis 2015)

1.	Worry, fear or anxiety
2.	Tiredness, exhaustion or fatigue
3.	Sleep problems/ nightmares
4.	Pain
5.	Eating or appetite
6.	Anger or frustration
7.	Getting around (walking)
8.	Memory or concentration
9.	Hot flushes/ sweating
10.	Sore or dry mouth

Accessed May 2022 https://www.macmillan.org.uk/_images/using-ehna-data-to-explore-needs_tcm9-298084.pdf

15.2.2 Common Post-HSCT Concerns

15.2.2.1 Physical Well-Being

Most studies found that survivors report resumption of routine physical activities but describe a greater number of medical problems (Mosher et al. 2009). Fatigue is one of the most commonly reported concerns, and many HSCT patients are dissatisfied with their energy levels many years after treatment. More recently, a systematic review (Oberoi et al. 2018) concluded that physical activity was effective at reducing fatigue in cancer and HSCT recipients and determining the best approaches for safe implementation should be a priority for further research.

Additionally, providing information materials and education on fatigue management is a key area where nurses can positively influence this troubling issue (Anderson et al. 2007; Andorsky et al. 2006).

15.2.2.2 Psychological Distress

It is known that 5–19% of HSCT survivors exhibit symptoms that are consistent with post-traumatic stress disorder (PTSD). In those without PTSD, four out of ten report clinically significant psychological distress at an average of 3.4 years post-transplant. The same study found that there was no difference by age, gender, transplant type or time following transplant (Rusiewicz et al. 2008). Kuba's more recent study (Kuba et al. 2017) investigated cancer-and-treatment-specific distress (CTXD) and its impact on symptoms of post-traumatic stress disorder (PTSD) in patients undergoing allogeneic HSCT. The results emphasise the major burden of uncertainty pre-HSCT and the impact of uncertainty and concerns regarding appearance and sexuality on PTSD symptomatology. Understanding the subtleties of psychological distress more generally (e.g. fear, guilt, loss of control) in HSCT patients is imperative to optimising the psychological well-being of this vulnerable population (Amonoo et al. 2020).

15.2.2.3 Return to Work (RTW)

HSCT survivors return to work despite ongoing physical and psychological symptoms. Younger

age and higher levels of education have been linked to a higher probability of post-transplant employment. Those who are unsuccessful in returning to work have poorer physical, cognitive and social functioning and report more pain, sleep disorders and distress (Mosher et al. 2009).

With this in mind, improving our understanding of the issues around work for these patients is highly relevant. Persoon et al. (2019) conducted a qualitative study to identify HSCT survivors' work perceptions; barriers to and facilitators of return to work (RTW); and possible solutions to improve RTW generating some important insights. RTW was often characterised as a complex and prolonged trajectory. Work perceptions varied between patients; most valued work as positive, but some also reported a decline in work capacity and/or in importance. Perceived barriers included treatment duration and side effects, presence of comorbidity and poor health pre-diagnosis and difficulties commuting. Perceived facilitators were financial incentives, keeping in touch with the workplace and support of other patients and family. Proposed solutions to improve RTW included discussing RTW at the hospital, enhanced employer support and improved access to rehabilitation programs.

While return to work or education is important to survivors, in guiding our patients, it is essential to consider the following:

- Type of work
  - Physical demand
  - Environment
  - Routine
  - Hours
- Support of employer
  - Phased return is usually the optimal way of enabling people to return to work progressively.
- Financial pressure
  - Many people need to return to work due to mounting financial difficulties.
- Self-esteem
  - Some people feel 'lost' without their work identity and feel a sense of urgency to return.

15.2.2.4 Sexuality

Evidence suggests that sexual function is one of the most prevalent and persistent long-term concerns after HSCT.

Despite its prevalence and the range of concerns that can be experienced across the entire sexual response cycle (El-Jawahri et al. 2018; Majhail 2017) sexuality and sexual function issues are under-reported. A range of sexual concerns have been described with a tendency for women to report more problems than men and women continue to describe more sexual concerns a number of years post-transplant (Mosher et al. 2009). Sexual function is typically multifactorial in origin with endocrine, mechanical and psychological factors. In their review on HSCT and sexuality, Thygesen et al. (2012) report on 14 quantitative studies that examined sexual function after HSCT. Sexual dysfunction is common following both autologous and allogeneic HSCT. Those that resume sexual relations in the first post-transplant year tend to experience fewer long-term issues (Jean and Syrjala 2009), but many survivors continue to experience profound sexual dysfunction even 5–10 years post-HSCT (Thygesen et al. 2012). The partners of patients who have undergone allogeneic HSCT are also negatively impacted. Poloméni et al. (2016) found that 75% of both patients and partners reported negative effects on their sexual life, and 30% of patients and 50% of partners reported negative effects on their couple life.

More recently, Gjærde et al. (2022) reported their European multicentre cross-sectional study of adult allo-HSCT recipients surviving >2 years and their partners. They focused on sexual functioning after transplant and evaluated whether a discussion of sexual functioning was perceived to have taken place between the transplant team and the survivor and partner. Of the 136 survivor and 81 partner participants, 47% of male and 65% of female survivors and 57% of male and 59% of

female partners reported clinically relevant sexual problems. Sixty-two percent of survivors and 79% of partners reported that sexual functioning had not been discussed with them during transplant. The impact of such high prevalence of sexual dysfunction warrants further investigation but also strategies to effectively prevent and treat sexual problems when they occur.

15.3 Addressing Sexuality

Sexuality is an important component of each person's life, whether they identify as male, female or non-binary, and is much more than the physical act of sexual intercourse or sexual expression. A key factor is to make no assumptions about the person or their sexuality or their choice of sexual expression. Make it clear to the person that you are willing to help and support them with any sexual concerns and questions. In a busy technical environment, the person may be seeking permission from those caring for them, to talk about these important concerns.

Sexuality is also about more hidden elements, including how people perceive themselves as sexual beings and the need to be recognised, respected, connected with, loved and cared for by others (Quinn 2010). Whether the person is in a relationship (gay, lesbian, heterosexual), is single or enjoys sex with one or multiple partners, most people will have sexual needs and desires throughout their lifespan (Oskay et al. 2014). There is a danger that in seeing sexuality as merely a physical expression that the haematology and transplant care team may fail to see that sexuality is about the whole person including how they relate to others in an intimate way (Oskay et al. 2014).

Whether the patient is or is not sexually active during the prolonged treatment period, before, during and after transplant, patients will need support and advice from the team caring for them, on sexual changes, choices and concerns. Sex and sexuality are largely seen as a very private matter, and a patient and/or partner may be reluctant to talk about their concerns or unexpected changes to a member of the transplant team who appear busy dealing with other aspects of the treatment process (Jean and Syrjala 2009, Roth et al. 2010, Mulhall 2008). It is important that the team makes it clear that they are there to help, and that support is available. There may be a misconception from some members of the transplant team that a person undergoing a stem cell transplant will not have an interest in sex. In reality, no matter what is happening in a person's life, all persons are sexual human beings (Quinn 2010). What that means for each person and how they will express that need throughout periods of their life may change and develop.

For some, people being sexually intimate with their partner during the treatment and transplant process may bring comfort, reassurance and hope, amidst ongoing uncertainty and change, while others will have no interest in being sexually active. However, feeling loved, accepted and cared for as one faces the uncertainty of transplantation may bring great comfort to the person and their partner (Jean and Syrjala 2009; Schover 1997).

In a busy haematology or transplant setting, the team can help to facilitate times of privacy when the individual can be alone or with their partner, if this is what they wish. The transplant team who recognise the importance of these intimate moments can often organise and plan treatments and interventions, at less acute points in the transplant process, in order to provide these moments or times of privacy. The diagnosis of any serious illness and the treatments and changes required may have a profound impact on the person and/or partner, affecting them physically, emotionally, socially and spiritually (Brandenburg et al. 2010). People may benefit from times of relaxation, massage therapy, aromatherapy or other complementary procedures.

Facing the reality of temporary or permanent infertility and the multiple body and life changes secondary to disease and treatments can affect a person's identity and how they perceive themselves. The physical and psychological demands of dealing with a serious illness, the transplant demands and setting, can interfere with the human sexual response cycle (desire/interest, arousal, readiness (penetration), orgasm and resolution, satisfaction). Any of these points on the response cycle may be affected, but these can be

sensitively addressed by a caring practitioner (Quinn 2010; Schover 1997).

15.3.1 Providing Support and Information

The team can sensitively support the person and the partner through the transplantation process and treatments, mindful of the impact on the person's sexual being. This includes providing accurate information on potential sexual changes that may occur, practical advice on the choice of treatment and interventions and a listening ear. Many sexual concerns arising in the haematology and transplant setting can be resolved or certainly reduced by a member of the team simply listening to the person's concerns and knowing how and where to access practical and expert help, if required (Katz and Dizon 2016; Quinn 2010). It is worth considering the impact of other co-existing morbidities, and the treatments required for these conditions on the person's sexuality and their ability to have sex.

In addressing sexual concerns, the transplant team can be proactive in supporting the person with body changes and psychological concerns. Members of the team who are aware of the possible impact that treatments, the transplant and supportive medications may have on a person's sexuality will be better able to speak to the person sensitively, honestly and clearly before the commencement of treatment. These issues should be an important part of the preparation for treatment and transplantation (Quinn 2010; Jean and Syrjala 2009).

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15.3.2 Addressing Fertility Concerns

Many of the chemotherapy agents used in the haematology and transplant setting can affect the person's fertility including alkylating agents which are known to cause most damage, resulting in either temporary or permanent infertility. For many young patients, this may be the first time that they have had to consider the possibility of planning children, and this will require support from the team, family and friends. Facing the possibility of being infertile can have a profound effect on how the person feels about themselves and their place in the world. Patients will be advised not to plan children during the treatment as the drugs and the demanding treatment requirements will affect the development of the embryo leading to foetal defects and miscarriage. For some people/couples, it may be very painful having to put their plans for a family on hold during the treatment and transplant period.

Occasionally a woman may discover a cancer diagnosis during her pregnancy and may be advised to undergo a medical termination because the pregnancy will not be viable and/or in order to proceed with necessary treatment. This can be a very difficult time for the woman and her partner; sometimes the full impact of this loss becomes more apparent following the completion of treatment. The team can be there to talk about the impact of treatment and to support and advice on the possible options available to support fertility (Schover 1997).

For men this may include sperm banking and the possibility of cryopreservation of testicular tissue, generally used for younger patients. For women, this may include cryopreservation of embryos or eggs and ovarian preservation. In some cases, the urgency of treatment may mean that fertility-saving options are not possible. During the transplant process, the focus for everyone including the patient may be on treating the disease, and the reality of being infertile becomes more important in the months and years following transplantation. This can be extremely difficult for patients who are beginning new relationships and have to disclose this to their new partner. This reality can be addressed at follow-up

clinics both in the hospital and community, ensuring the person has support that they can access. Individuals and couples may need support and advice over their concerns of having passed or passing on genes to their children predisposing them to a higher risk of cancer (Quinn 2010).

Support may take the form of practical advice, including adjusting to an altered sex life during treatment, adequate pain/symptom control, comfortable positioning during sex, contraception, providing private moments, advice on sexual aids and medical treatments or simply an opportunity to talk about concerns and fears (Table 15.2). Practical support and guidance can help the person returning to sexual activity after transplantation or simply regaining confidence in being sexually expressive again.

Many of the treatment agents (chemotherapy, targeted therapies and radiation) used in the field of haematology and transplantation are known to cause specific problems which can lead to lower sex drive, vaginal dryness (which may cause pain during intercourse), erection concerns, ejaculation and orgasm difficulties (which may lead to loss of confidence and lack of sexual enjoyment) (Brandenburg et al. 2010). Some drugs including the vinca alkaloids and some targeted therapies may cause nerve damage giving rise to erectile dysfunction and to ejaculation and orgasm difficulties. Following total body irradiation, a small number of patients may experience damage to the nerve, vascular and muscle tissue giving rise to possible erectile difficulties, including the inability to get or maintain an erection suitable for sexual penetration or vaginal changes including stenosis and/or dryness which may cause pain during sexual intercourse. Women may benefit from the team explaining the use of vaginal lubricants and dilation to prevent vaginal stenosis.

Table 15.2 Providing support (Quinn 2010)

Sensitively listening and addressing fears
Creating time and privacy for couples to be alone
Providing adequate symptom relief
Support with body changes
Encouraging couples/sexual partners to talk to one another
Advice on creative foreplay (hugging, stroking, having a shared bath, kissing, mutual masturbation)
Advice on alternative positioning
Alternatives to sexual penetration
Guidance on sexual aids (dilators, vacuum pumps, dildo, toys)
Guidance on medical treatments (oral, injection, pellets)
Counselling

Men may require support in exploring treatment options for erectile concerns. These complications may require interventions including advice on oral medications (sildenafil, tadalafil, vardenafil), pellet (intraurethral alprostadil) (MUSE), injection (intracavernosal alprostadil) and appliances (vacuum device) to address erectile dysfunction (Katz and Dizon 2016).

Hormone replacement therapy unless contraindicated may have a role to play, alongside, an opportunity to talk through fears and concerns and/or psychosexual therapy support (Brandenburg et al. 2010). If patients are sexually active during treatment, the team may advise them to use some form of barrier method (condoms, femidoms, dental dams) (Quinn 2010). This is to prevent pregnancy and to protect the patient's partner from the minimal risk of irritation caused by a small amount of chemotherapy agents remaining in bodily fluids such as semen, urine and rectal and vaginal secretions. These barrier methods may also reduce the risk of infection especially if the patient is at risk of neutropenia and prolonged immunosuppression. While individuals are advised to take steps to prevent infection, rarely should this prevent the person from enjoying sex with a partner. Occasionally the team may learn of partners no longer sleeping in the same bed for fear of contamination to their partner; the team can reassure the couple that this is not necessary and they can continue with their usual sleeping arrangements.

Other sexual difficulties may arise due to body changes and other symptoms including weight gain or loss, skin changes, graft versus host disease, constipation, diarrhoea, nausea, fatigue, oral complications, depression and anxiety. The person's confidence in being sexually active may be affected by the unwanted body changes that occur (Katz and Dizon 2016).

Poorly controlled symptoms, such as nausea, vomiting, constipation, diarrhoea, loss of appetite and extreme tiredness caused by the treatments and the underlying disease, may affect the person physically and psychologically. Carefully assessing and managing these symptoms may enable the person to enjoy the comfort of sexual intimacy with their partner (Katz and Dizon 2016).

Some of the supportive treatments used in the transplant setting while bringing relief to these unpleasant symptoms can also give rise to sexual difficulties. Pain relief including opiates may give rise to uncomfortable constipation, tiredness, nausea and mucosal dryness leading to painful vagina/anal intercourse and erectile dysfunction. Some anti-sickness medication while providing necessary relief from nausea can effect erectile functioning. While anti-anxiety and anti-depressant mediations help with stress and anxiety, these medications can lead to a lower sex drive and erectile dysfunction (Quinn 2010).

Some patients will be at risk of bleeding due to thrombocytopenia and should be advised to continue a sex life if they so wish but to be aware of reducing trauma during sex, including vaginal, oral and anal intercourse. Localised trauma may be reduced by using a more gentle thrusting movement during penetration or masturbation. Many of the drugs used in the transplant setting may bring on the early onset of menopause and the associated symptoms which can cause great distress.

Medically induced menopause brings unwanted symptoms including vaginal dryness, mood changes, hot flushes, low confidence and sometimes a lack of interest in sex. Women may find it more difficult to achieve a satisfactory orgasm (Brandenburg et al. 2010; Jean and Syrjala 2009). It is important that women and their partners are forewarned about these symptoms but also to ensure these issues are revisited sensitively during and after treatment.

Men, women and non-binary persons may need support and advice on finding alternative ways to express themselves sexually both during and after transplant. Although people may have a reduced interest in sex for a period of time, their interest in returning to a sexually active relationship may return in weeks and months following the transplant. Practical measures including the careful positioning of medical devices may enable a person to be held and hugged during prolonged hospitalisation. These measures also include reducing clutter around the persons' bed so that their partner can be closer to them and critically reviewing and removing any unnecessary infection control measures that may act as a barrier to intimacy. Practical advice on how to deal with medical devices including urinary catheters and emptying bowels and/or bladder before having sex can provide greater comfort.

While the person may lack the energy to participate in penetrative sexual intercourse, they may wish to try alternatives including cuddling, hugging, lying in bed together, increased time for foreplay, sharing a bath or shower together and sharing quiet and private moments together. Although the sexual needs of patients in the highly technical setting of transplantation can sometimes be overlooked, the ability to be intimate with a partner might be a welcome relief from some of the demands made on the person by the transplant process.

15.4 Summary

15.4.1 Wider Impact of Survivorship Care

Carers of those undergoing stem cell transplant report high levels of emotional distress (Wulff-Burchfield et al. 2013). The psychological difficulties that carers report can be prolonged. This is exacerbated by their own lifestyle and role disruption; carers report financial difficulties and are often unable to work for periods themselves or have to give up work altogether due to their 'carer role' commitment (Beattie and Lebel 2011). It is important to recognise these issues and offer carers support, information and invest in their preparedness for caregiving to improve their experience (Winterling et al. 2021).

15.4.2 Models of Long-Term Follow-Up

It is widely recognised that HSCT recipients require structured long-term follow-up and screening to reduce the morbidity and mortality demonstrated in those considered as long-term survivors.

There are clear guidelines around screening requirements (Majhail et al. 2012) but little direction on how these might best be implemented in a late effects (LE) service. A survey of UK transplant centres identified that all had a LE service and most had a standard operating procedure outlining its process but identified wide variability in almost every aspect of the late effects services (Hamblin et al. 2017). A follow-up survey in 2019 identified improvements in number of centres having dedicated long-term follow-up clinics and associated SOPs. However, there was ongoing variation in vaccination programmes, access to cancer screening and audit processes (Dignan et al. 2021).

Important components for successful delivery of LE service include:

- Assessment tools incorporating clinical and psychosocial late effects.
- Availability of a range of medical and allied health specialists.
- Access to psychological services.
- Implementation of second malignancy screening, e.g. mammography and PAP smear.

15.4.3 Opportunities for Nurses

Nurses have a significant role in delivering and/or coordinating post-HSCT care for patients.

Nurses have an opportunity to:

- Identify useful resources for patients.
- Develop post-HSCT services for patients.
- Ensure that care meets the needs and concerns of patients.
- Develop innovative roles as individual practitioner and as part of a wider multidisciplinary team.
- Develop the evidence base by leading/participating in survivorship research.
- Develop creative ways of working and providing suitable clinical and supportive care.

15.5 Post-transplant Complications and Surveillance

Standardisation of follow-up protocols is important to prevent important tests being overlooked or being duplicated unnecessarily.

15.5.1 Second Malignancies

There is an increased risk of developing a second solid cancer post-transplant in the range of 2–6% at 10 years. Data suggests that second solid cancers occur twice as frequently in the transplant population than in the general public with this increasing to threefold at 15 years. There are several risk factors that may contribute to the development of a second solid cancer (Curtis et al. 1997; Tichelli et al. 2019):

- Use of TBI or prior radiotherapy
- Primary disease
- Male sex
- Pre-transplant conditioning
- Genetic predisposition contributing to initial cancer and subsequent malignancy
- Older age at transplant
- Donor gender (F > M)
- Immune dysfunction (T-cell depletion, HLA mismatched, allo-HSCT, GvHD, immunosuppressive therapy)

Clinicians have long been aware that radiation leads to second solid cancers with a latent period of approximately 3–5 years before developing a malignancy (Rizzo et al. 2009). The risk for non-squamous cell cancer is higher in younger patients (especially those under 30 years) at ten times that of nonirradiated patients. Other cancers such as breast, thyroid, brain, central nervous system, bone and connec-

tive tissue and melanoma are all related to radiation exposure. Screening for some of these cancers is available and aids in early diagnosis (Savani et al. 2011).

All patients should be enrolled into national cancer screening programmes for breast, cervical, colon and skin cancer. Particular attention should be paid to women who receive radiation to their chest >800 cGy to ensure they follow guidelines laid down for paediatric survivors. These state that annual mammogram screening should begin at 25 years of age or 8 years after exposure whichever occurs later. Women should have PAP smears annually to three yearly, and those with GvHD should be screened annually. Patients should have at least six monthly dental reviews and an annual thyroid assessment, and if any thyroid nodule is identified, imaging and potential biopsy should be undertaken (Savani et al. 2011).

At the initial consent for transplant consultation, patients should be counselled about the future potential risks of second malignancy. This is an ideal time to engage with the patient and help them make changes to their lifestyle that will have an impact on their lives moving forward. Smoking cessation, a healthy balanced diet, taking regular exercise, reducing alcohol consumption and taking care of their skin in the sun will all have beneficial effects.

15.5.2 Systematic Post-transplant Screening and Investigations

A specific screening plan for transplant patients has been published by Majhail et al. (2012) on behalf of the Center for International Blood and Marrow Transplant Research (DeFilipp et al. 2016), American Society for Blood and Marrow Transplantation (ASBMT), European Group for Blood and Marrow Transplantation (EBMT), Asia-Pacific Blood and Marrow Transplantation Group (APBMT), Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ), East Mediterranean Blood and Marrow Transplantation Group (EMBMT) and Sociedade Brasileira de Transplante de Medula Ossea (SBTMO).

These comprehensive guidelines written by an expert group were last updated in 2011, published in 2012 and have been the mainstay of long-term follow-up care worldwide. They provide a consensus for screening and preventative measures for autologous and allogeneic stem cell transplant patients who have survived for at least 6 months following transplant. However, with continuing advances in treatment and supportive care, growing knowledge and expertise in this area, updated guidance is much in need. At the time of writing, the new guidelines are on the horizon and will continue to inform and influence models of late effects care to benefit patient outcomes. There are also patient versions of the guidelines that can be found at www.bethematch.org/patients-and-families/life-after-transplant/ (accessed May 2022).

The recommendations take each system and describe the late complication and the general risk factors for developing them. It includes suggested monitoring tests and preventative measures that should be undertaken supported by associated evidence from randomised trials and if none is available from retrospective studies or from expert opinion when no evidence exists at all (Majhail et al. 2012).

Infection and revaccination are described elsewhere in this textbook, but regardless of time since transplant, all presentations of infection should be thoroughly and rigorously investigated and treated aggressively. Revaccination should be initiated as per the widely accepted Ljungman et al. (2009) guidelines.

Majhail et al. (2012) elegantly describe the general follow-up that a transplant patient should receive in a systematic order and this can be applied fairly easily in the clinic environment. Below is a concise form of the guidance. Please refer to Table 15.3 for the recommended screening guidelines and the full publication for further details.

15.5.3 Ocular Screening

Ocular screening should commence at 6 months and continue on an annual basis for assessment of

Table 15.3 Recommended screening and prevention (Majhail et al. 2012) printed with permission from Elsevier Inc

Recommended screening/prevention	6 months	1 year	Annually
Immunity			
Encapsulated organism prophylaxis	2	2	2
PCP prophylaxis	1	2	2
CMV testing	2	2	2
Immunisations	1	1	1
Ocular			
Ocular clinical symptom evaluation	1	1	1
Ocular fundus exam	+	1	+
Oral complications			
Clinical assessment	1	1	1
Dental assessment	+	1	1
Respiratory			
Clinical pulmonary assessment	1	1	1
Smoking tobacco avoidance	1	1	1
Pulmonary function testing	+	+	+
Chest radiography	+	+	+
Cardiovascular			
Cardiovascular risk-factor assessment	+	1	1
Liver			
Liver function testing	1	1	+
Serum ferritin testing		1	+
Kidney			
Blood pressure screening	1	1	1
Urine protein screening	1	1	1
BUN/creatinine testing	1	1	1
Muscle and connective tissue			
Evaluation for muscle weakness	2	2	2
Physical activity counselling	1	1	1
Skeletal			
Bone density testing (adult women, all allogeneic transplantation recipients and patients at high risk for bone loss)		1	+
Nervous system			
Neurologic clinical evaluation	+	1	1
Evaluate for cognitive development		1	1
Endocrine			
Thyroid function testing		1	1
Growth velocity in children		1	1
Gonadal function assessment (pre-pubertal men and women)	1	1	1
Gonadal function assessment (post-pubertal women)		1	+
Gonadal function assessment (post-pubertal men)		+	+
Mucocutaneous			
Skin self-exam and sun exposure counselling	1	1	1
Gynaecologic exam in women	+	1	1
Second cancers			
Second cancer vigilance counselling		1	1
Screening for second cancers		1	1
Psychosocial			
Psychosocial/QOL clinical assessment	1	1	1
Sexual function assessment	1	1	1

Majhail et al. (2012)
1 recommended for all transplantation recipients, *2* recommended for any patient with ongoing cGvHD or immunosuppression, + reassessment recommended for abnormal testing in a previous time period or for new signs/symptoms

keratoconjunctivitis sicca syndrome, cataracts and ischaemic microvascular retinopathy. Sicca syndrome (vaginitis, dry skin and xerostomia) occurs in 10–40% of patients.

15.5.4 Oral Examination

The oral cavity can be affected by chronic graft versus host disease (cGvHD) and, even in the absence of cGvHD, requires repeated assessment from 6 months especially if there is a sign of xerostomia (dry mouth) as this increases the risk of dental caries. Good oral hygiene and treatment of oral infections should be initiated promptly on recognition. There is an increased risk of secondary oral squamous cell carcinoma in those with oral cGvHD, and patients should be aware to raise concerns.

15.5.5 Pulmonary Screening

Respiratory problems include bronchiolitis obliterans syndrome (BOS), idiopathic pneumonia syndrome (also known as interstitial pneumonitis), cryptogenic organising pneumonia (COP) and sinopulmonary infections. Clinical review at 6 months and annually with physical examination and history should be performed. Counselling with regard to smoking cessation is extremely important. If the patient has GvHD, then it may be appropriate to undertake pulmonary function testing, and if there is evidence of lung involvement, then imaging such as inspiratory and expiratory CT for air trapping to exclude BOS is indicated.

15.5.6 Cardiovascular Tests

Cardiovascular disease is rare in the transplant setting. Clinical review at 6 months and annually with physical examination, blood pressure monitoring and history should be performed. Counselling with regard to a healthy lifestyle, taking regular exercise, maintaining a healthy weight, eating well and not smoking should be reinforced in clinic and be in line with the recommendations for the general public. Risk factors such as diabetes, hypertension and dyslipidaemia can be addressed with non-medication interventions, but some may require treatment if this approach is unsuccessful. If any concerns are raised, investigations with ECG and ECHO and referral to cardiology may be needed.

15.5.7 Hepatic Complications

Liver function tests are taken at most clinical reviews and aid assessing for the onset of GvHD. Patients with pre-existing liver conditions such as hepatitis B or C should have monitoring of their viral load by polymerase chain reaction (PCR) and referral to a hepatologist or virologist for advice on ongoing antiviral therapy. Serum ferritin levels should be measured at 1 year, and those with elevated levels should be followed more closely and considered for chelation.

15.5.8 Renal Surveillance

Renal injury is common post-transplant as many drugs are nephrotoxic such as ciclosporin, aminoglycosides, aciclovir, etc., and renal function should be checked at 6 months and annually thereafter. In those with chronic kidney disease (CKD), referral to nephrology and assessment with renal ultrasound and/or biopsy should be considered.

15.5.9 Musculoskeletal Assessment

Patients with GvHD and especially those receiving systemic steroids may encounter problems with muscle strength, general weakness and loss of function. All patients should be given advice about regular daily exercise. Those who have developed GvHD should be assessed for a range of joint movement to detect sclerotic changes and referred on to physiotherapy for active intervention.

Osteoporosis is common with reports of incidence of 25–50% at 18 months (Majhail et al.

2012). Those with ongoing GvHD requiring long-term use of corticosteroids are at particular risk. DEXA scanning is indicated and advice regarding diet and exercise given to optimise bone mineral density and falls prevention. Supplementation with vitamin D and calcium may be required.

15.5.10 Neurological Assessment

All patients should be assessed annually for signs and symptoms of neurologic deficit such as leukoencephalopathy, cognitive impairment or neurotoxicity as a consequence of long-term use of calcineurin inhibitors. Also any signs or symptoms of peripheral neuropathy should be examined for. If any deficit is found during routine assessment, the patient should be referred for nerve conduction studies or MRI as indicated by the clinical findings. A referral to a neurologist may be appropriate.

15.5.11 Endocrine Surveillance

Endocrine dysfunction is common following stem cell transplant. Thyroid function and gonadal testing are recommended at 1 year and then annually with replacement if needed. Up to 25% of patients who receive total body irradiation will have some thyroid dysfunction (Majhail et al. 2012). Significant gonadal failure requiring hormone replacement is more common in women than men as the ovaries are more sensitive to the effects of chemoradiotherapy than the testes. Sexual dysfunction and assessment of sexual function are described more fully in this chapter. Sexual dysfunction is common although typically under-reported and results in impaired quality of life (QoL) and relationship problems.

15.5.12 Second Malignancy Screening

All patients should be counselled regarding the increased risk of secondary cancers and advised to monitor themselves frequently (skin, breast and testicular examination) and report symptoms promptly. The median time to development is 5–6 years post-therapy although this risk continues to rise with no plateau. Cancers of all organs are well described but the skin, oral cavity, CNS, bone, thyroid and connective tissue are more prevalent. Breast screening should be carried out for women who receive total body irradiation at age 25 or 8 years following exposure whichever is later but no later than 40 years. Cervical PAP smears should be performed every 1–3 years (yearly if presence of GvHD) in women aged 21 and over or within 3 years of initial sexual activity whichever is earliest. Advice regarding sun exposure, wearing sun screen, loose fitting clothing and a hat and glasses when outside should be given to all patients.

15.5.13 Psychological Screening

Psychological problems may manifest in various ways in the post-transplant setting, and clinicians need to be vigilant for subtle signs and make appropriate referrals for interventions. Depression, anxiety, fatigue and psychosexual dysfunction are frequently observed. This often increases in the transition from early transplant recovery to longer-term follow-up as the patient adjusts to the change in life style, employment and financial independence. Relationships with family and friends may change leading to distressing outcomes. Adopting a standardised approach to psychosocial assessment using validated tools can be helpful to offer validation and discussion airtime for patients experiencing psychosocial sequelae.

A low level of suspicion should be maintained by the clinician for early signs of psychological distress throughout follow-up.

15.5.14 Fertility Concerns

Fertility is often lost due to high-dose treatments although not in all. Patients should be counselled thoroughly regarding safe sex in those of childbearing age. Those who are contemplating pregnancy should be referred to specialist services for advice and monitoring.

15.5.15 Summary

There is no standard instrument guiding post-transplant care that will apply to all patients who have undergone stem cell transplant. Each patient is an individual, and, as such, an individualised plan needs to be generated. Large institutions have published guidelines, such as Fred Hutchinson Cancer Research Center's LTFU guidelines, the National Marrow Donor Program Be The Match long-term survival guidelines, the Livestrong Care Plan and the Passport for Cure, to name but a few.

The key message is that early standardised screening leads to early detection and treatment or increased monitoring, although it is not fully proven that this leads to better outcomes. It is the role of all healthcare providers to raise awareness for potential secondary effects of high-dose therapies and to ensure adequate and appropriate survivorship care. Empowering patients to be involved in their own long-term care is paramount. Having 'buy-in' from the patient will help to ensure that they remain vigilant for subtle changes and attend screening appointments. They have self-interest at heart and are less likely to forget that they require certain follow-up tests if they are educated regarding the importance of screening and monitoring in the late effects clinic.

Having a written care plan or treatment summary detailing the chemotherapies, radiation and side effects experienced with future dates for screening is ideal and can be based on any of the published material listed above. Educate the patient and family on what can be expected and when, enable them to become an active participant in their own post-transplant care and provide ongoing support to help our patients navigate the potentially stormy waters ahead.

15.6 Metabolic Syndrome

In addition to the more familiar post-HSCT sequelae, metabolic syndrome (MetS) is of particular note due to its collection of cardiovascular risk factors that increase the risk of cardiovascular disease, diabetes mellitus and all-cause mortality. Metabolic syndrome (MetS) is typically defined as a clustering of five factors including (1) hyperglycaemia, (2) hypertriglyceridaemia, (3) low high-density lipoprotein (HDL) cholesterol, (4) hypertension, (5) obesity (measured by high waist circumference) [International Diabetes Federation, Alberti KGMM, et al. Alberti et al. 2009]. The long-term survivors of HSCT have a considerable risk of developing MetS and subsequently cardiovascular disease.

Indeed, an EBMT cross-sectional, multicentre, noninterventional study of 453 adult HSCT patients surviving a minimum of 2 years post-transplant attending routine follow-up HSCT and/or late effects clinics in 9 centres (Greenfield et al. 2021) found the overall prevalence of MetS was 37.5% rising to 53% in patients >50 years of age at follow-up. In this study, no differences were observed in rates of MetS between autologous and allogeneic HCT survivors, nor any association with graft versus host disease (GvHD) or current immunosuppressant therapy. Furthermore, there was a significantly higher occurrence of cardiovascular events (CVE, defined as cerebrovascular accident, coronary heart disease or peripheral vascular disease) in those with MetS than in those without MetS (26.7% versus 9%, $p < 0.001$, OR 3.69, 95% CI 2.09–6.54, $p < 0.001$), and, as expected, MetS and CVE were age-related.

A series of recommendations (Table 15.4) have been developed (DeFilipp et al. 2016) to

Table 15.4 Screening guidelines for metabolic syndrome (DeFilipp et al. 2016)

Screening guidelines for metabolic syndrome and cardiovascular risk factors for adult and paediatric patients among the general population and HCT survivors				
	General adult population	Adult long-term HCT survivors	General paediatric population	Paediatric long-term HCT survivors
	(http://www.uspreventiveservicestaskforce.org/)	Majhail et al.	(http://www.nhlbi.nih.gov)	Pulsipher et al.
Weight, height and BMI	Weight height and BMI assessment in all adults (no specific recommendation for screening interval)	No specific recommendations	Weight, height and BMI assessment after 2 years of age (no specified screening interval)	Weight, height and BMI assessment yearly
Dyslipidemia	For persons with increased risk for coronary heart disease, assessments should begin at age 20.	Lipid profile assessment every 5 years in males aged ≥35 years and females aged ≥45 years	Lipid panel between 9 and 11 years of age or earlier if family history	Lipid profile at least every 5 years; if abnormal, screen annually
	The interval for screening should be shorter for people who have lipid levels close to those warranting therapy, and longer intervals for those not at increased risk who have had repeatedly normal lipid levels	Screening should start at age 20 for anyone at increased risk (smokers, DM, HTN, BMI ≥30 kg/m^2 and family history of heart disease before age 50 for male relatives or before age 60 for female relatives)		
Blood pressure	Blood pressure assessment every 3-5 years in adults aged 18-39 years with normal blood pressure (<130/85 mm hg) who do not have other risk factors	Blood pressure assessment at least every 2 years	Blood pressure assessment yearly after the age of 3 years, interpreted for age/sex/height	Blood pressure assessment at each visit and at least annually
	Blood pressure assessment annually in adults aged ge1; 40 years and for those who are at increased risk for high blood pressure (blood pressure 130 to 139/85 to 89 mm hg, those who are overweight or obese, and African-Americans)			
Hyperglycaemia	Screening for abnormal blood glucose (HbA1C, fasting plasma glucose or oral glucose tolerance test) every 3 years in adults aged 40-70 years who are overweight or obese	Screening for type 2 DM every 3 years in adults aged ≥45 years or in those with sustained higher blood pressure (>135/80 mm Hg)	Fasting glucose every 2 years after the age of 10 years in overweight children with other risk factors	Fasting glucose at least every 5 years; if abnormal, screen annually

BMI body mass index, *DM* diabetes mellitus, *HbA1C* haemoglobin A1C, *HCT* haematopoietic cell transplantation, *HTN* hypertension

help clinicians provide screening and preventive care for MetS and cardiovascular disease among HSCT recipients. Furthermore, all HSCT survivors should be advised of the risks of MetS and encouraged to undergo the recommended screening based on their predisposition and ongoing risk factors.

15.7 Adherence in the Long-Term Follow-up Setting

Adherence issues are common in HSCT survivors. Adherence describes the extent to which survivors follow the medical recommendations. Adherence is not limited exclusively to medication but it encompasses all health-related behaviours that are recommended by healthcare providers (Eeltink and Kisch 2021).

Causes for non-adherence are often beyond the patient control with adoption of unhealthy behaviours further influenced by multiple interacting factors. Among those quoted in the literature are the patient's physical discomfort, misunderstanding and uncertainty about the merits of medication or monitoring, poor communication regarding the diagnosis and treatment regime and inadequate information on illness in general and secondary effects of the disease and its treatment in particular.

*Five factors of adherence (*WHO 2003):

1. Health system
2. Socio-economic
3. Health or condition
4. Treatment
5. Patient

1. Health System

   A relationship based on a partnership between the patient, relatives and the treating physician improves adherence (Russmann et al. 2010). Insufficient and inadequate doctor/patient/family dialogue, relationship, trust and mutual information are quoted as one of the most important causes of noncompliance.

   Poor attention to patient education with regard to medication benefits and risks, side effects and correct dosing can result in decreased quality of life, more frequent consultations and possible hospital readmissions. More broadly and beyond medication adherence alone, a whole team approach to education and support facilitates the development of joint strategies that increase likelihood of adherence.

2. Socio-economic

   Barriers to adherence may revolve around a lack of resources, both in the patient's finances and in the level of clinical knowledge and expertise and medical facilities available.

   The economic cost of cancer plays a significant role in therapy adherence. Many patients need to travel considerable distances to access treatment or care at substantial personal cost. Furthermore, the majority of patients and many of their carers are unable to work during and for many months following treatment leading to a loss of income and a lack of financial stability.

   Availability of social support services is yet another potent factor, especially in patients overwhelmed by multiple pressing needs.

3. Health or Condition

   Extensive symptoms such as nausea, vomiting, pain, constipation and fatigue play an important role in a person's ability to manage medication and follow a treatment course with a degree of reliability. High symptom burden or other physical conditions similarly impacts on attendance and ability to adopt healthy behaviour strategies.

   Disease progression and declining health can interfere with the physical ability to manage treatment and also the willingness to continue with treatment.

4. Treatment

   Therapy-related factors refer to the treatment regime and the process of taking medication according to the regime. Working to optimise adherence requires precision and concentration and the ability to follow specific instructions around timing of dosing. Often careful planning around the daily programme of treatment will increase the patient's ability to follow the treatment plan accurately.

   Drug frequency, odour, side effects and prior experience of therapy can all impact upon and hinder adherence (Lee et al. 1992).

5. Patient

   The patient's attitude towards their illness and treatment are important factors. Their support network, resources, disease knowledge, health beliefs and expectations are central to the degree to which they will be able to follow treatment.

   Psychological distress or other psychological factors can also be a cause, often requiring professional intervention and support.

   For many, a simple lack of understanding of the importance of regular treatment or assessment is the driver for poor adherence or attendance. Others are afraid that annual check-ups may reveal sinister pathology that they would prefer to ignore.

15.8 Immunisations Following Stem Cell Transplantation

Stem cell transplant and CAR-T recipients lose their pre-existing immunity within weeks to vaccine-preventable diseases and are at increased risk of morbidity and mortality (Kamboj and Shah 2019). Therefore, all stem cell transplant and CAR-T recipients should be routinely revaccinated once T and B cell immunity has sufficiently recovered.

Tables 15.5 and 15.6 describe the ECIL 2017 updated guidelines for vaccination of haemopoietic stem cell transplant recipients (Cordonnier et al. 2019).

For those patients who develop graft versus host disease (GvHD), it is likely that all immune function and protection are lost. Cordonnier et al. (2019) recognise the difficulty of a higher risk of infection and the protection that vaccines offer, but that vaccines may not be effective if used too early in this patient group. There is little data and the recommendation is to follow the same revaccination schedule but advocate measuring antibody levels pre- and post-vaccine to determine the level of cover that has been achieved and the need for any boosters.

Family members should continue to have all of their routine vaccinations to help avoid infection transmission to the patient (Cordonnier et al. 2019).

15.8.1 CAR-T Considerations

In 2019 best practice recommendations were written for adults and children undergoing CAR-t cell therapy by EBMT and JACIE. The guidelines were updated in 2021 and are currently in press. The revaccination of this patient group is not yet fully understood. There is consensus that vaccination may offer benefit and follow that of transplant patients, but should be in line with national standards and individual patient risk (Yakoub-Agha et al. 2019).

15.8.2 COVID-19

Guidelines for patients post-transplant and CAR-T may vary by country, please follow national guidance. Advice for the UK by the Joint Committee on Vaccination and Immunisation and supported by BSBMTCT states that patients vaccinated pre-CAR-T or transplant should be revaccinated with 3 primary doses. These should occur from 2 to 6 months in transplant and 3 to 6 months following CAR-T. Dosing schedule can be found at: https://www.gov.uk/government/publications/third-primary-covid-19-vaccine-dose-for-people-who-are-immunosuppressed-jcvi-advice/joint-committee-on-vaccination-and-immunisation-jcvi-advice-on-third-primary-dose-vaccination

Table 15.5 ECIL 7 recommendations for vaccination of haemopoietic stem cell transplantation recipients with inactivated vaccines page 202

	Recommendation and (grading) in allogeneic HSCT	Recommendation and grading in autologous HSCT	Paediatric specificities
PCV13*	From 3 months after transplantion three doses of PCV13 (or subsequent, broader spectrum, conjugate vaccines) are recommended at 1-month intervals (A I); in case of chronic GVHD, considering the low response to PPSV23, an additional dose of PCV instead of a dose of PPSV23 is recommended 6 months after the third dose of PCV is administered (B II u)	Same initial schedule as for allogeneic HSCT: three doses of PCV13 administered from 3 months after transplantation at 1-month intervals (A I)	The same schedule is recommended in children and adults; children with transplants usually have a similar response to healthy children,[22] and respond better than adults, but often develop vaccine-related fever and local reactions[28]
PPSV23*	12 months after the procedure, if the patient does not have chronic GVHD that requires immunosuppressors, then one dose of PPSV23, not earlier than 8 weeks after the last PCV is recommended (B I)	One dose of PPSV23 at 12 months after transplantation and not earlier than 8 weeks after the last PCV (B I)	The same schedule is recommended for children and adults
Hib vaccine*	From 3 months after transplant three doses at 1-month intervals are recommended (B II r); no preference on the type of vaccine (conjugated with tetanus-protein or diphtheria-protein). Alternatively, to decrease the overall number of vaccine doses administer three doses of a combined diphtheria-tetanus-pertussis-Hib vaccine from 6 months after the transplantation (BIIr)	Same recommendation and same grading as for allogeneic HSCT	The same schedule is recommended for children and adults; children usually respond better than adults[6]
Neisseria meningitidis vaccines*	From 6 months after transplantation at least two doses of either a monovalent or tetravalent C vaccine (B II u) and meningococcal B vaccine (B III), in accordance with country recommendations for a given age and particularly for at-risk groups such as students living in campus, travellers, or soldiers	Same recommendation and grading as for allogeneic HSCT	The same schedule is recommended for children and for adults; children and adolescents are the main at-risk population
Tetanus-diphtheria vaccine*	From 6 months after the transplant three doses at 1–2-month intervals (B II u); DT vaccines should be preferred over Td vaccines both in children and adults (C III); booster doses should be administered according to country recommendations	Same recommendation and grading as for allogeneic HSCT	The same schedule is recommended for children and for adults; children and adolescents are the main at-risk population
Acellular pertussis vaccine*	The addition of pertussis toxoid to the diphtheria-tetanus vaccine, three doses at 1–2-month intervals, should be considered (CIII); although there is no specific study with DTaP in adult HSCT recipients, considering the poor response to Tdap, the DTaP that contains a higher dose of pertussis toxoid than the Tdap should be preferred both in children and adults (C III)	Same recommendation and grading as for allogeneic HSCT	The same schedule is recommended for children and for adults; previously unvaccinated HSCT infants should be vaccinated as soon as possible; children seem to respond better than adults
Inactivated influenza vaccine IIV†	From 6 months after transplantation a seasonal IIV dose should be administered annually at the beginning of flu season, after the first years following transplant, and at least until 6 months after stopping any immunosuppressor and as long as the patient is judged to be immunocompromised (A II r) or life-long (B II r); a second dose administered 3–4 weeks after the first one could be considered in patients with severe GvHD or low lymphocyte counts (B II r); in the setting of a community outbreak, IIV can be administered 3 months after transplantation, in which case, a second dose administered 3–4 weeks later is likely to be beneficial (B II r)	From 6 months: annual seasonal IIV, 1 dose, at the beginning of influenza season, at least as long as the patient is judged to be immunocompromised (B II r); in the setting of a community outbreak, IIV can be administered 3 months after transplant, in which case, a second dose administered 3–4 weeks later is likely to be beneficial (B II r)	Children aged 6 months to 8 years, receiving IIV for the first time after transplantation should receive a second dose at least 4 weeks after the first dose (B II t); for children older than 9 years, a second dose of vaccine after 3–4 weeks could be considered in patients with severe GVHD or low lymphocyte counts (B II r)
IPV	From 6 to 12 months: three doses of IPV are recommended to be administered at 1-2-month intervals (B II u); booster doses should be administered according to country recommendations	Same recommendation and grading as for allogeneic HSCT	The same schedule is recommended for children and for adults; children usually respond better than adults; however, because of a higher risk for losing polio immunity in the years after initial vaccination for patients transplanted before the age of 10 years, we recommend a regular assessment of anti-polio antibody titres to assess persistent immunity and consider boosters
HBV vaccine*	Before transplant patients who are negative for all HBV markers that are transplanted with a graft from an anti-HBc positive donor should be vaccinated if possible (B III) and could additionally receive anti-HBV immunoglobulins; 6 months after transplantation patients who were negative for HBV before transplantation and patients who were vaccinated before transplant but lost their immunity at 6 months should be vaccinated according to country recommendation (6–12 months after transplantation 3 doses should be administered 0, 1, and 6 months apart), (B II t); patients infected with HBV before HSCT (HBsAg negative and anti-HBc positive) should be assessed regularly for anti-HBs antibody titres and should be vaccinated if they have unprotective titres (B III); if anti-HBs titres are <10 mIU/mL 1–2 months after the initial series of three vaccine doses, an additional series of three doses should be considered	6 months after transplantation: patients who were negative for HBV before transplantation and patients who were vaccinated before transplantation but lost their immunity after 6 months should be vaccinated according to country recommendation and age (6–12 months after transplantation 3 doses should be administered 0, 1, and 6 months apart)(B II t); patients infected with HBV before HSCT (HBsAg negative and anti-HBc positive) should have anti-HBs antibody titres assessed regularly and be vaccinated if they have unprotective titres (B III); if anti-HBs titres are <10 mIU/mL 1–2 months after the initial series of three vaccine doses, an additional series of three doses should be considered	The same schedule is advised for children and for adults, except that children should receive a standard paediatric dose (10 μg) of vaccine and adolescents should receive 20 μg of the vaccine according to the summary of product characteristics of each vaccine
HBV vaccine*	6–12 months after transplantation recommendations for the general population in each country should be followed (B II u)	Same recommendation and grading as for allogeneic HSCT	Follow age recommendations for general population in each country

aP=acellular vaccine. GvHD=graft-versus-host disease. HSCT=haemopoietic stem cell transplantation. PCV13=13-valent pneumococcal conjugate vaccine. PPSV23=23-valent polysaccharide pneumococcal vaccine. HPV=human papillomavirus. IPV=inactivated poliomyelitis vaccine. HBV=hepatitis B virus. Hib=*Haemophilus influenzae* type b. IIV-inactivated influenza vaccine. DT vaccines=diphtheria-tetanus vaccines containing high-doses diphtheria toxoid. Td vaccines-diphtheria-tetanus vaccines containing low-doses diphtheria toxoid. *Guideline proposed on the basis of laboratory endpoints. †Guideline proposed on the basis of clinical endpoints. For the evidence-based medicine grading system (A I, A IIr, B I, B III, B II u, B II t, B II r, C III) see appendix.

Patients who should receive a booster dose will be greater than 24 months and did not have immunosuppression or GvHD at the time of their first or second dose, full guidance found at:

https://www.gov.uk/government/news/jcvi-issues-updated-advice-on-covid-19-booster-vaccination

Table 15.6 ECIL 7 recommendations for vaccination of haematopoietic stem cell transplantation recipients with live-attenuated vaccines page 206

	Recommendation and (grading) in allogeneic HSCT	Recommendation and grading for autologous HSCT	Paediatric specificities
LAVV*†	LAVV is contraindicated in HSCT recipients with active GvHD, a relapse of the underlying disease, or ongoing immunosuppression (DIII); at least 24 months after transplantation one dose of LAVV can be considered in VZV seronegative adult patients with no GVHD, no ongoing immunosuppression, no relapse of the underlying disease, and no treatment with immunoglobulins during the previous months‡ (B II r); the addition of a second dose in adults could be considered in patients who were seronegative before HSCT or had no history of VZV infection	Same recommendation as after allogeneic HSCT	Two doses (instead of one dose in adults) of LAVV can be considered in children meeting the same imitation criteria as adults (B II r); abel specific recommendations should be followed for the amount of time between administering the two doses
Zoster LAVT†	Not recommended (D III)	Not recommended (D III)	Not recommended (D III)
MMR§	From 24 months after HSCT, recipients should have MMR antibody titres tested (B II u); consider vaccination only in patients with no GvHD, no immunosuppression, no relapse of the underlying disease, and treatment with immunoglobulins during the previous monthst; seronegative patients for measles should receive one dose of MMR (B II u); HSCT recipients who are women, seronegative for rubella, and of childbearing potential should receive one dose of MMR with the same precautions (C II u); in case of a measles outbreak, MMR vaccination could be considered 12 months after transplantation in patients with low-grade immunosuppression (C III)	Same recommendation as after allogeneic HSCT	Because of a lower response in children, two doses—instead of one in adults—should be considered in children, at least 4 weeks apart
Yellow fever§	Yellow fever vaccine should be considered cautiously and only administered to patients with no active GVHD and no immunosuppressive drugs, and if the patient cannot avoid traveling to endemic area before (DIII) or from 24 months (CIII) after the procedure	Yellow fever vaccine should be considered cautiously if the patient cannot avoid traveling to endemic area before (DIII) or from 24 months (CIII) after the procedure before (DIII) or from 24 months (CIII)" after the procedure	Although there are no data in children, the same schedule is recommended for children and for adults

HSCT=haemopoietic stem cell transplantation. LAVV=live attenuated varicella vaccine. LAV=live attenuated vaccine. GvHD=graft-versus-host disease. VZV=varicella-zoster virus. MMR=measles-mumps-rubella. *Guideline proposed on the basis of laboratory endpoints. †All LAV are contraindicated as long as the patient is considered severely immunocompromised. ‡The interval between the last immunoglobulin administration and the administration of a varicella or MMR live-attenuated vaccine should be at least 3 months, ideally between 8 and 11 months. For the evidence-based medicine grading system (B II u, B II r, C II u, C III, D III) see appendix. §(Guideline proposed on the basis of clinical endpoints.

15.9 End-of-Life Care in the Haematopoietic Stem Cell Transplant (HSCT) Setting

15.9.1 Background

The writings of Viktor Frankl (Frank 1947) and Martin Heidegger (1962) are a reminder that death is not separate from life and in fact, death is an essential component of life. By acknowledging this reality, each individual is able to choose life each day and to make choices that are important for them. For many nurses working in the field of HSCT, this reminder to live a worthwhile life is perhaps part of the driving force to practice nursing and to continue engaging with person-centred care (McCormack 2020). Amidst the great advances in HSCT including the increasing cure rates, people living longer and better management of toxicities, the reality still remains, that some people will die of their advancing disease and/or treatment-related factors.

While the majority of the patients will return home to continue living their lives, some of the adults and children cared for in this setting may die within the hospital or transplant ward, or be discharged home to die. In the highly clinical and technical setting of HSCT, this reality can sometimes be overlooked and avoided, leaving the patient and family feeling abandoned and alone (Quinn 2020, Randall & Downie 2006). In a study exploring the experience of living with advanced cancer, some participants spoke of feeling misunderstood and left alone with their advanced disease. A large part of their suffering arose from the interpretation of their personal distress that was not easily visible to others, and many participants felt that people did not fully understand what

they were going through, leaving them feeling ultimately alone (Quinn 2020).

However, despite these challenges, the delivery of good end-of-life care can be improved through some simple measures and approaches (Stevens et al. 2009, Randall and Downie 2006). Each member of the HSCT team (clinical and non-clinical), who has come to know the patient and family, often over a prolonged period of time is invited to recognise and to respond to their important role in supporting patients and their families at this crucial time in their lives. When curative treatment is no longer an option and the focus moves towards more compassionate focussed care and the management of symptoms, the trusting relationship between the patient, family and the HSCT team is crucial.

15.9.2 End-of-Life Care

End-of-life care and the care of those who are dying has been defined as care that helps all those with advanced, progressive, incurable illness to live as well as possible until the day they die (World Health Organisation 2020). Unfortunately, many healthcare workers in HSCT settings may find it difficult to discuss the reality of dying due to a lack of knowledge and skills, avoidance, fear of upsetting the patient and themselves, and the overmedicalisation of the dying process (Quinn 2022). In reality, care for those moving towards the end of life in the HSCT setting calls for a combination of clinical and human skills, built on sensitivity and humility, coupled with good symptom management, core values within nursing care and practice (Quinn 2022).

Important and sensitive conversations about the reality that treatment is no longer working and exploring what the patient and family would like as they approach the end of life need to be addressed. The reluctance to engage with this conversation may be exacerbated as a result of living in a society that tends to distance itself from this sensitive subject, coupled with the fact that the reality of death touches us all (Elias 1985). The following principles of good end-of-life care or a personal commitment to those moving towards the end of life may be worth considering in the HSCT setting:

A commitment to those facing the end of life.

- When you are moving towards the end of life, we will be honest with you and sensitively support you and your family to ensure your needs and wishes are met, and you are enabled to die in your preferred place of care.
- When you are approaching the end of your life, we will offer you the opportunity to be involved in your care planning. This will include an assessment of your needs and preferences and an agreed set of actions reflecting these choices.
- We will work to ensure that you and your family receive excellent care in accordance with your wishes, at all times of day and night. We will work with our community partners to ensure this happens.
- We will offer you personalised care, based on your wishes and needs. This will include attending to your physical, social, emotional, spiritual and religious needs.
- We recognise the importance of your family, your friends and your support network, and they have the right to have their own needs assessed and reviewed and to have a carer's plan.
- In order to care for you and your family, we will ensure that all staff and volunteers working in our team are aware of the issues surrounding care at the end of life, in particular the importance of excellence in communicating.
- We will participate in research in order to improve patient and family care at the end of life in the HSCT setting.

(Quinn 2020)

This commitment from the HSCT team relies on identifying when a patient may have incurable disease and/or untreatable complications, having the courage to sensitively broach the subject of dying with the patient and family, working with the patient and family to identify and address their physical, social emotional and spiritual needs and planning care together. These core

principles can support nurses, doctors and the HSCT team to support the patient to receive, the right care, in the right place, and at the correct time (Quinn et al. 2017).

15.9.3 Care for those Who Are Dying

The ability to help the person who is dying and to identify what is important to them has been described as an art, and like all creations of art, this form of art takes time (Table 15.7). All nurses, doctors and health care workers working in HSCT will be required to use this art through practising the principles of palliative or supportive care (Table 15.8).

15.9.4 Managing Symptoms

Mindful that good end-of-life care requires the team to attend to the person and their physical, social, spiritual and emotional needs and concerns, some of the common symptoms seen in the end-of-life care setting include those seen in Table 15.9.

Pain continues to be one of the symptoms that people with advanced disease fear and yet research clearly shows that pain management is not always achieved in a consistent and robust manner (Quinn et al. 2021). This may be as a result of a number of reasons including poor communication, a lack of knowledge of what is meant by pain, which drugs to use, the best therapeutic doses, non-pharmacological approaches and failing to understand what pain means to the individual. While pain is often classified as nociceptive, neuropathic, refractory, breakthrough, chronic or acute and this is important to consider when assessing pain and choosing treatment options, pain can also be understood in a more human manner, as a disturbance or a disruption in key relationships (Table 15.10). This approach helps the HSCT team to appreciate some of the more hidden aspects of pain and how other challenging symptoms can impact on the individual. Rarely will the person's experience of pain happen in isolation from other symptoms/factors including anxiety, fear, loss, fatigue, breathlessness and the inability to sleep or eat. While pain

Table 15.7 The art of assessment (Quinn 2022)

Paying attention to the person and hearing their priorities
Thinking beyond the symptom to how it affects the person
Creating time and being present
Cocreating a plan of care with the person and family
Applying 'skilled companionship'[a]
Intervening and reviewing to monitor symptom support and management

[a]Skilled companionship has been described by Alastair Campbell (1984) as the ability to use our clinical skills as nurses and doctors and our humanity to support a person as they strive to cope with the reality of living with advanced disease

Table 15.8 Principles of palliative/supportive care

Providing relief from pain and other distressing symptoms
Intention not to hasten or postpone death
Integrating the physical, psychosocial and spiritual needs of patients and family
Offering a support system to support the family before and after death
Using a team approach including counselling and chaplaincy
Improving quality of life directing treatment, preventing unnecessary and distressing tests or treatments

(World Health Organisation 2020; Quinn and Thomas 2017)

Table 15.9 Common symptoms in end-of-life care

Pain (physical, social, emotional, spiritual)
Nausea
Vomiting
Oral problems (dryness, ulcers, mucositis)
Anorexia/cachexia
Agitation/restlessness
Diarrhoea
Excessive secretions
Ascites
Breathlessness
Anxiety/distress
Depression
Confusion
Feelings of loss and grief
Aloneness
Spiritual/religious abandonment

can exacerbate a person's anxiety and their inability to sleep, the inability to sleep and the presence of worry can increase the personal experience of pain and make the pain harder to manage; all of these need to be considered. By taking a more person-centred approach (physical, social, emotional and spiritual) to symptom management, better control may be achieved.

(Quinn et al. 2016)

Following the principles of good pain management, a combination of pharmacological approaches (Randall and Downie 2006) which may include paracetamol, non-steroidal anti-inflammatories, opiates, corticosteroid, anti-depressants, anti-epileptics, antimuscarinics and benzodiazepines should be considered and reviewed and increased as required (Quinn et al. 2015). Pain relief should be prescribed on a regular basis and prescribed as needed for 'breakthrough pain'. The HSCT team should also consider the best route of administration (oral transdermal, subcutaneous, sublingual, buccal mucosa, intravenous) for the patient and derived benefit.

Pharmacological approaches should be complemented with non-pharmacological interventions including massage, touch, pastoral/spiritual support, hearing the patient's concerns, music and relaxation approaches. A combination of both is often the best approach to managing total pain or indeed any symptom in advanced disease (Table 15.11). 'To ignore psychological and spiritual aspects of care may often be the reason for seemingly intractable pain' (Watson et al. 2011. 18).

The management of these and other symptoms commonly seen in this setting including nausea, agitation and excessive secretions should also consider both a pharmacological and non-pharmacological approach focussing on what suits the individual patient.

The following tool (Fig. 15.1) has been designed to encourage patients to talk about their personal experience of pain and what it means to them, but it may also be used to help the patient to talk about their impact of other symptoms. The tool is designed to invite the patient to talk about what is important to them including the reality of their own dying process and their fears and concerns.

Following the principles of the WHO pain ladder (Fig. 15.2), a combination of pharmacological approaches which may include paracetamol, non-steroidal anti-inflammatories, opiates, corticosteroid, anti-depressant, anti-epileptic, anti-muscarinic and benzodiazepine should be considered and reviewed and increased as required. Pain relief should be prescribed on a regular basis and prescribed as needed for 'breakthrough pain'. The HSCT

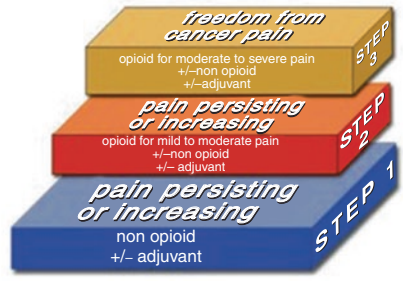
Table 15.10 A human approach to understanding pain and other symptoms (a disturbance or disruptions in key relationships)

Physical pain	A disturbance or disruption in the relationship between the person and their body
Social pain	A disturbance or disruption in the relationship between the person and their world including their family, work and society
Emotional pain	A disturbance or a disruption in the relationship between the person and their emotions or how they see themselves
Spiritual pain	A disturbance or disruption in the relationship between the person and their beliefs and values

Table 15.11 Examples of drugs and approaches used in the last days of life

Pain	Morphine/diamorphine/oxycodone/alfentanil/fentanyl +/− adjuvant drugs (corticosteroid, anti-depressant, anti-epileptic, anti-muscarinic, benzodiazepine)	Human touch, complementary therapies, prayer, mindfulness, silence, presence
Excessive secretions	Glycopyrronium	Positioning, suctioning (with caution)
Nausea	Levomepromazine/ondansetron/metoclopramide/cyclizine	Removal of distressing smells
Agitation	Midazolam	Presence, touch, spiritual/pastoral support
Breathlessness	Morphine, benzodiazepines, oxygen	Positioning, open windows, fan

Fig. 15.1 Aspects of pain/other symptoms and what they mean to the individual are often hidden from view and take longer to identify and manage (Managing Advanced Cancer Pain Together—An expert guidance. MACPT (2016) http://www.macpt.eu [Accessed June 2022])



World Health Organization. Cancer pain ladder for adults; http://www.who.int/cancer/palliative/painladder/en/. [Accessed 13th Nov 2016]

Adjuvant options

- Corticosteroid
- Antidepressant
- Anti-epileptic
- Anti-muscarinic
- Benzodiazepinec

Fig. 15.2 Using the WHO approach to pain management in the HSCT setting (Copyright © MACPT. All rights reserved http://www.macpt.info/)

team should also consider the best route of administration (oral transdermal, subcutaneous, sublingual, buccal mucosa, intravenous) for the patient and derived benefit. Pharmacological approaches can be complemented with non-pharmacological interventions including massage, touch, pastoral/spiritual support, hearing the patient's concerns, music and relaxation approaches. A combination of both is often the best approach to managing total pain or indeed any symptom in advanced disease. 'To ignore psychological and spiritual aspects of care may often be the reason for seemingly intractable pain' (Watson et al. 2011. 18).

15.9.5 Support

An important aspect of end-of-life care is recognising the HSCT team's role in supporting the patient and their family but also knowing when the person may require more expert help including pastoral care, psychological support and specialist palliative care for challenging aspects of symptom management and/or support/advice for the HSCT team. Compassionate care in the end of life setting can be described as the nurse's ability to pay attention to the person living with advanced disease and 'be present' while listening and responding to any issues that they may have

(Quinn 2020). While a nurse may not always be able to remove the cause of someone's distress, taking time to listen may act as a palliative measure and alleviate their distress (Quinn and Thomas 2017). Using a compassionate approach to assessment and care enables the nurse to explore with the person how their symptoms and/or concerns are affecting them and what type of assistance they may require.

Pastoral, psychological and palliative/supportive care should be seen as a core part of HSCT care and introduced to the patient much earlier so that these approaches are seen as complementing the treatment approach of HSCT. While an individual may not have any religious affiliation or religious needs, many patients may require someone to listen to their hopes and dreams, their concerns and fears (Purjo 2020). The HSCT team with careful planning, support and working with the patient's community medical and nursing team can in many cases enable patients with advanced disease to be cared for in their own home if that is the patient's wishes. While focussing on the person with advanced disease, the team is well placed to support family members including children and parents.

Those involved in the dying process, including nurses, doctors and the wider healthcare team may be affected by loss. Team members may have witnessed deaths of people they have come to know over a period of time, and they may need to take steps to care for themselves. This type of personal self-care might include discovering a space or an activity, where each team member can find solace and support. Those who have found ways of caring for themselves may be best placed to care for others who are dying or experiencing grief (Quinn 2022).

15.9.6 Conclusion

Although the current trend in health care appears to be one of delivering more care with less resources, this in no way negates the central focus on delivering truly holistic patient-centred care. We can no longer continue to talk about patient-centred care without a willingness to engage with all aspects of the person we support and care for including their physical, emotional, social, existential and spiritual needs. Moving beyond a medical approach to treatment and care in the HSCT setting to one of attending to the person can bring great comfort and support. Often, the greatest gift a nurse or doctor can give to those who are dying is their attention and presence. Amidst the uncertainty and the painful realities each person has to face, caring is often perceived as occurring when another person carries out a simple act of kindness with a caring attitude (Quinn 2020).

15.10 Late Effects and Long-Term Follow-Up in Paediatric Patients

The study of late effects after paediatric haematopoietic stem cell transplantation (HSCT) offers unique opportunities and challenges, magnified by the fact that children going through each developmental stage (infant, toddler, child preadolescent and young adult) have different sensitivities to therapies, resulting in different complications. For instance, infants and toddlers are susceptible to neurocognitive damage with radiation, and adolescents are at high risk of joint/bone issues with steroid therapy (Baker et al. 2011).

Paediatric HSCT survivors have a higher cumulative incidence of late effects compared to the studies of cancer survivors who did not receive HSCT as part of their treatment, with 93% of survivors having at least one late effect with a median follow-up of only 7 years (Bresters et al. 2010).

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) improves event-free survival in acute myeloid leukaemia (AML); however, the burden of late effects may be increased.

In general, allo-HSCT survivors reported a significantly higher burden of late effects in several organ systems and more frequent use of medications than the CT (chemotherapy only) survivors (Wilhelmsson et al. 2019).

Children who undergo HSCT with TBI have a significant risk of both growth hormone deficiency (GHD) and the direct effects of radiation on skeletal development. The risk is increased with single-dose TBI as opposed to fractionated TBI, pre-transplant cranial irradiation, female gender and post-treatment complications such as graft versus host disease (GVHD).

Late side effects and complications can include chronic immunosuppression and infections, chronic GvHD, bronchiolitis obliterans, endocrine dysfunction, cataracts, disease recurrence and secondary malignancies (Tomlinson and Kline 2010).

The endocrine system is highly susceptible to damage by high-dose chemotherapy and/or irradiation prior to haematopoietic stem cell transplantation (HSCT) during childhood. Insufficiency of thyroid hormone is one of the most common late sequelae of HSCT and occurs more often in young children. Deficiency in the pituitary's production of growth hormone is a problem of unique concern to the paediatric population (Dvorak et al. 2011).

Survivors who are transplant recipients have higher risks of subsequent malignancies involving epithelial and mucosal tissues (Leisenring et al. 2006).

15.10.1 Specific Late Effects After HSCT in Childhood

15.10.1.1 Growth Impairment

Impaired linear growth after HSCT is multifactorial in origin and can be due to growth hormone deficiency (GHD), hypothyroidism, hypogonadism, corticosteroid treatment as well as poor nutritional status, genetic factors and metabolic status. Because of these confounding factors, the reported prevalence of growth impairment varies widely (9–84%) between studies (Baker et al. 2011).

Treatment includes thyroid replacement therapy and growth hormone therapy, respectively, for thyroid dysfunction and growth delays (Tomlinson and Kline 2010).

Growth hormone deficiency (GHD) replacement therapy provides the benefit of optimising height outcomes among children who have not reached skeletal maturity (Chemaitilly and Robison 2012).

Even though myeloablative conditioning regimens for HSCT are known to affect endocrine function, Myers et al. (2016) recently evidenced that 'poor growth, thyroid dysfunction and vitamin D deficiency remain prevalent despite reduced intensity chemotherapy for haematopoietic stem cell transplantation in children and young adults'.

15.10.1.2 Neurocognitive Impairment

There is limited evidence of neurocognitive and academic outcomes in paediatric HSCT:

- HSCT seems to pose a low risk overall.
- Risk increases for children of age < 5 years at the time of SCT who received TBI (Phipps et al. 2008).

The procedure of SCT entails probably minimal risk of late cognitive and academic sequelae. Subgroups of patients are at relatively higher risk: patients undergoing unrelated donor transplantation, receiving TBI and those who experience GVHD. No significant changes are seen in global intelligence quotient and academic achievement (Phipps et al. 2008).

Despite substantial exposure to potentially neurotoxic agents, studies have generally shown survivors of paediatric HSCT to be within normal limits in cognitive and academic functioning, and with stable performance over time, although children who are younger at the time of transplantation may be at increased risk for cognitive impairment (Phipps et al. (2008)).

Phipps et al. (2008) reported 158 patients who survived and were evaluated at 1, 3 and 5 years' post-transplant and concluded that HSCT, even with TBI, poses low to minimal risk for late cog-

nitive and academic deficits in patients who are at least 6 years old at the time of transplantation.

However, socio-economic status was found to be a significant determinant of all cognitive and academic outcomes.

15.10.2 Return to School

It could be hypothesised that children beginning the elementary school with important delays in fine and gross motor domains could be more at risk for academic achievement. Moreover, longer hospitalisations and necessary treatments like HSCT contribute to limit the discovering of motor functioning at this age stage forcing the young patients to stay in bed and to avoid social and physical contacts due to their immunocompromised status (Taverna et al. 2017).

A diagnosis of cancer during the teenage years arrives at an important stage of development, where issues of normality, identity and independence are crucial. Education provides opportunity for peer contact, achievement and development for teenagers.

Key areas involved in the impact of a cancer diagnosis on teenagers' educational engagement include school attendance, reintegration and peer relationships. Long-term school absences are a concern for teenagers but do not necessarily lead to a reduction in educational and vocational attainment. It is important to involve healthcare and education professionals, as well as parents and teenagers themselves, in school matters (Pini et al. 2012).

Factors that may place children and teens at increased risk for difficulties in school (Landier et al. 2013) include:

- Diagnosis of cancer at a very young age
- Numerous prolonged school absences
- A history of learning problems before being diagnosed with cancer
- Cancer treatment that results that reduced energy levels
- Cancer treatment that affects hearing or vision
- Cancer treatment that results in physical disabilities
- Cancer treatment that includes treatment of the central nervous system

Collaborative education planning should be initiated on diagnosis and aim to include nonacademic variables, such as peer groups, which can influence successful maintenance of education. Further research is needed to understand the relationship between education engagement and teenagers' cancer experiences as a whole, as well as gaining a more in-depth understanding of how teenagers experience their education after a diagnosis of cancer (Pini et al. 2013).

It will therefore be imperative that we continue to follow our HSCT survivors on a long-term basis and continue research efforts to study long-term outcomes (Baker et al. 2011).

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