The A-B-C of Haematopoietic Stem Cell Transplantation

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SUMMARY

Haematopoietic stem cell transplantation (HSCT) has progressed rapidly since its introduction about five decades ago. There is now an increasing demand for transplant physicians in both public and private domains to perform this procedure in view of significant improvement of remission rates in haematological malignancies and increasing indications of HSCT. Peripheral blood has largely replaced bone marrow as the preferred source of haematopoietic stem cells (HSC). Transplantation-related mortality and morbidity rates have considerably decreased because of improved conditioning regimens, human leukocyte antigen (HLA) typing methods, supportive care, and most importantly, prophylaxis, diagnosis and treatment of serious infections. New transplantation strategies, such as reduced intensity transplantation, have extended the use of allogeneic transplant to patients with older age and co-morbidities. Current efforts are focused on ways to increase the donor pool and to improve the long term outcome of HSCT survivors in particular to reduce the relapse rate and the late effects of HSCT. This article summarizes the sources and procurement of HSC, the types and process of HSCT, indications for HSCT and complications associated with HSCT with particular reference to the current practice within the local settings.

KEY WORDS:
Haematopoietic stem cell transplantation, Autologous, Allogeneic, Bone marrow transplant, Peripheral blood stem cells, Cord blood stem cells

INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) refers to any procedure where haematopoietic stem cells (HSC) of any donor type and any source are infused to a recipient with the intention of repopulating or replacing partly or totally the recipient's haematopoietic system[1]. Dr ED Thomas pioneered this field whereby his team performed the first allogeneic SCT in a patient with end-stage leukaemia[2]. Since then, HSCT has progressed in leaps and bounds in various aspects including source of stem cells, types of donors and conditioning regimens. In fact, its indications are no longer in haematological malignancies only, but have expanded to some of the incurable congenital and acquired diseases of the haematopoietic system and other non-haematological disorders (Table I). This advancement has also extended to the third world countries, for example Malaysia, with its first allogeneic bone marrow transplantation performed in University of Malaya in a child in 1987 and in an adult in 1993[3]. Up to December 2008, a total of 468 autologous, 982 allogeneic and 9 syngeneic adult and paediatrics HSCTs were performed in all transplant centres in Malaysia[4].

HSC have unique biological properties, including their capacity to proliferate and self-regenerate in the lymphohaematopoietic system, their ability to migrate to the bone marrow spaces following intravenous infusion and their ability to maintain viability following cryopreservation, prolonged freezing and thawing process prior to re-infusion[5].

HSCT can be classified according to the[5]:

- Donor type ["autologous" (auto)-patient's own cells, "syngeneic"-from an identical twin, "allogeneic" (allo)-from a non-identical donor]
- Relationship between donor and recipient ("related" or "unrelated")
- Degree of HLA-matching between donor and recipient ["matched" or "mismatched"]; haplo-identical HSCT may now be performed, often from a parent donor to a child recipient)
- Anatomical source of the stem cells ("bone marrow', "peripheral blood' or "cord blood")
- Type of conditioning regimen ["myeloablative" (standard) or "non-myeloablative" (reduced intensity)]
- Type of graft manipulation (if any) (e.g. "T-cell depleted", "tumour cell purged")

Sources of haematopoietic stem cells (HSC)

Stem cells can be harvested from bone marrow (BM), peripheral blood (PB) and cord blood (CB). According to latest data in National Transplant Registry of Malaysia, a total of 511 bone marrow alone, 823 peripheral blood alone, 53 cord blood alone, 10 combined bone marrow and cord blood, and 61 combined bone marrow and peripheral blood stem cell transplantations were performed up to December 2008[4]. When HSCT was first developed, BM was the only available source of stem cells. A $CD34^+$ cell dose of 3 x 10^6/kg or more (which may require up to of 0.5-1.5 litres of BM) has been associated with successful engraftment, decreased transplant-related mortality, and improved overall survival In HLA-identical sibling BM transplantation[6,7]. The procedure is tedious as multiple marrow aspirations need to be performed and donors are subjected to general anaesthesia. There is a possibility that the BM cells are contaminated by the tumour cells in autologous collection, which is a source of relapse.

Due to these limitations, researchers tried to find alternative source of stem cells. HSC constitute a very small amount in the peripheral blood of a healthy donor (less than 0.1% of all

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nucleated cells)[8]. These HSC are identified by their immunophenotypic features and thus can be measured as CD34+ cells. In the steady-state situation, BM and PB stem cells are in equilibrium with each other[8]. Therefore, this allows the stem cells to migrate from extravascular marrow sites to PB and *vice versa*. CD34+ stem cells concentration in PB is approximately 3.8 ± 0.8 x 10^6/L which is too low to be harvested[9]. However, these HSC can be mobilized from the BM into the PB by systemic administration of granulocyte-colony stimulating factor (G-CSF) with or without chemotherapy and are subsequently collected via leukocytopheresis[8]. Apart from increasing the number of cells, G-CSF causes the release of proteases that degrade the proteins that anchor the stem cells to the marrow stroma, causing their release into the PB[10]. Following G-CSF administration, there is 16- to 23-fold increase in PB CD34+ stem cells over the baseline[9]. A minimum threshold of 2 x 10^6 CD34+ cells/kg in the PBSC collection has been associated with prompt engraftment and can be achieved in one to two sessions of leukapheresis[8]. Following collection, PBSCs are then processed and can be cryopreserved for months to years. The main advantage of PBSCT as compared with BMT is faster engraftment of the haematopoietic cells in the bone marrow, probably because of the higher content of committed haematopoietic precursor cells[10]. This will result in shorter hospitalization time and lower overall cost of the procedure. Nevertheless, there is an increased risk of chronic graft-versus-host disease (GvHD) in allogeneic PBSCT[1].

At birth, the human umbilical cord blood (UCB) contains rates of $CD34^+$ cells similar to those observed in normal BM and are therefore considered as an alternative source of cells for HSCT[1]. There is no risk to the donor as the collection of UCB takes place after the delivery of the newborn and placenta and the cord is appropriately clamped[11]. The first successful CB transplantation was performed by Dr E Gluckman in 1988 in a boy with Fanconi's anaemia using umbilical cord blood collected at the birth of his sibling[12]. Since then, the use of CB has rapidly increased due to several favourable factors (Table II). However, the major limitation of CB stem cells is that the amount that can be collected is small and transplantation in an adult might need multiple cord blood donors. One of the advantages of UCB is easy procurement. There is a low risk of viral transmission of cytomegalovirus (CMV), hepatitis and human immunodeficiency virus (HIV)[11]. A higher degree of mismatch is also acceptable with a lower risk of acute and chronic GvHD as CB is relatively deficient in mature T-cells[11].

Types of HSCT

a) Autologous

Autologous transplantation is used as a method of infusing patient's own stem cells which was harvested earlier as a rescue therapy after high-dose myeloablative therapy[5]. The aim of administration of high-dose chemotherapy is to eradicate the remaining tumor cells. This is followed by subsequent rescue of the host's bone marrow with previously collected autologous HSC (Figure 1). As there is no risk of graft rejection or GvHD, immunosuppressive agents are not required.

b) Allogeneic

In allogeneic HSCT, stem cells harvested from another person are infused into the patient following high dose chemotherapy, whereby donor and recipient are not immunogenically identical (Figure 1). The preferred donors are human leukocyte antigens (HLA)-matched sibling donors. In the pre-transplant work-up, class I and class II HLA antigen compatibility is tested via serological or molecular techniques and compared between the patient and siblings. Class I includes HLA-A, HLA-B and HLA-C while Class II includes HLA-DR, HLA-DP and HLA-DQ. Fully HLA-matched matched sibling has all HLA loci identical to the recipient and this will reduce the possibility of GvHD and graft failure. However, an HLA-matched sibling donor is only available in 30-40% of patients[13]. In the absence of matched sibling donors, several alternatives of allogeneic transplantation are nowadays available which include matched unrelated donors (MUD), unrelated umbilical cord blood (UCB) or haploidentical donors (3 out of 6 HLA alleles mismatched).

Other factors to be taken into consideration in choosing a donor are donor age (younger is better), sex (female stem cells given to a male is less favorable), cytomegalovirus (CMV) serology (CMV-negative has better outcome), pregnancy and transfusion history (preferably lower parity and no history of miscarriage), donor-recipient blood group compatibility and body weight[14]. Immunosuppression is very crucial and needs to be monitored closely. This is to prevent GvHD and graft rejection without risking the stem cells engraftment. Two most common immunosuppressive drugs are methotrexate and cyclosporine which can be used alone or in combination.

In the post-transplantation period, donor-recipient chimaerism studies need to be performed. This can be done via fluorescent-in-situ hibridization (FISH) studies of sex chromosomes (for donor and recipient with different gender), short tandem repeats (STR) analysis or variable number of tandem repeats (VNTR) analysis.

Conditioning regimens

In general, conditioning therapy must be given prior to stem cell infusion. Conditioning regimens can be myeloablative (standard) or nonmyeloablative (reduced intensity). The aim of myeloablative conditioning is eliminate the malignant cells and make space in the bone marrow for the infused stem cells to regrow and expand. Common myeloablative regimens used in ALL and AML patients are cyclophosphamide-total body irradiation (CyTBI) and busulfan-cyclophosphamide (BuCy), respectively[15].

In nonmyeloablative conditioning regimen, the aim is to induce immunosuppression in the recipient's system so that donor cell engraftment can take place and exert graft-versus-tumour effect. This less toxic approach enables HSCT in elderly patients and patients with organ dysfunction who cannot tolerate full myeloablative conditioning[10]. One of the most commonly used protocols is fludarabine-busulfan-anti-T-cell immunoglobulin (FluBuATG) as suggested by Slavin *et al*[16]. The advantages and disadvantages of both autologous and allogeneic HSCT are described in Table III.

Complications of HSCT

Complications of HSCT can be generally divided into conditioning-related or immune-related. Both myeloablative and nonmyeloablative conditioning regimes may cause early (within 30 days) complications such as nausea, vomiting, mucositis, alopecia and interstitial pneumonitis. Cyclophosphamide may cause haemorrhagic cystitis which may manifest as dysuria and haematuria. Late conditioning-related complications include endocrine problems such as infertility, premature ovarian failure and osteoporosis, and risk of secondary malignancies such as AML and solid organ tumours.

A potentially fatal early complication is veno-occlussive disease (VOD), also known as sinusoidal obstruction syndrome. The incidence has been reported to be as high as 70% with a mortality rate up to 70%[17]. It is caused by damage to the sinusoidal endothelium, resulting in sinusoidal obstruction, necrosis of hepatocytes in zone 3 of liver acinus and narrowing and fibrosis of central veins[17]. Predisposing factors include conditioning with total body irradiation or busulfan, preexisting liver disease, hepatotoxic drugs and certain genetic mutations[17]. Patients present with tender hepatomegaly, weight gain, ascites and predominantly direct hyperbilirubinaemia within the first 30-60 days. Diagnosis is based on clinical suspicion as there is no specific non-invasive tool available at the moment. There is no standard effective therapy at present. Defibrotide may be effective treatment for severe VOD but prospective randomized studies are required[17].

Immune-related complications may develop within months to years after HSCT due to suppressed host immunity. Infection remains a leading cause of death among allogeneic transplants and is a major cause of morbidity among autologous HSCT. The preventive measures include conducive physical environment, isolation procedures, neutropaenic diet, care of central venous lines, antimicrobial prophylaxis and vaccination. The type, timing and duration of antibacterial, antifungal and antiviral prophylaxis used depend on the type of transplantation and the degree of immunosuppression.

Allogeneic transplant recipients may develop characteristic infections during the three different phases post HSCT (Figure 2). During the first phase, the aplastic period, the risk of infection is mediated mainly through neutropaenia and damage to the mucocutaneous barriers as a result of conditioning regimen and frequent vascular access requirements[18]. Hence, oral, gastrointestinal and skin flora are the sources of infection which is commonly bacterial in origin. During the second phase which is the phase of acute GvHD, impaired T-cell function predominates causing delayed immunologic recovery and prolonged immunodeficiency[18]. Therefore, HSCT recipients are more vulnerable to opportunistic viral and fungal infections[18]. Meanwhile, the third phase is characterized by B-cell dysfunction in combination with T-cell dysfunction in patients with chronic GvHD[18]. Hence they are at greater risk for serious bacterial infections such as the encapsulated organisms in addition to the similar opportunistic viral and fungal infections.

In autologous HSCT recipients, the aplastic phase is similar to the allogeneic recipients. However, the most important difference is the better T-cell function in autologous SCT. After engraftment, most patients will be at lower risk of infection.

Despite new advancement of antimicrobial therapy, bacterial infections still pose a major problem in HSCT patients especially in the febrile neutropaenia phase. Prevalences of Gram-negative bacilli such as *Pseudomonas aeruginosa, Escherichia coli* extended spectrum β-lactamase (ESBL), and *Stenotrophomonas maltophilia*, as well as Gram-positive cocci such as methicillin-resistant *Staphylococcus aureus* have increased at many institutions[18]. Inappropriate use of antibiotics is known to cause the emergence of these bacteria. Since HSCT patients are immunocompromised, broad spectrum antibiotics such as carbapenems, third to fourth generation cephalosporin such as cefepime with or without vancomycin are indicated as empirical therapy. Cultures must be taken from all possible sites of infection as soon as possible prior to administration of antibiotics.

The timing of invasive fungal infections (IFI) is bimodal distribution, with peak that is correlated with prolonged neutropaenia (pre-engraftment) and GvHD (late recovery period). Patients who have undergone cord blood HSCT and T-cell depleted HSCT are especially at high risk of developing IFI[19]. Identification of glucan and galactomannan, the antigens from the fungal cell walls, coupled with high-resolution computed tomography (HRCT) has enabled early diagnosis and treatment of IFI leading to a significant drop in mortality rates[19].

Viral infections caused by *Herpes simplex* occur early in the course of transplantation while cytomegalovirus (CMV) infection usually occurs after engraftment[18]. The prevention of CMV disease is essential since the results of therapy for proven CMV pneumonia are still poor. Involvement by CMV in the gastrointestinal tract (GIT) may be confused with the development of GvHD and warrants upper and/or lower endoscopic examination and biopsy.

Vaccination

To prevent late infections as a result of suppressed recipient immunity that can persist for months to years after HSCT, a guideline for revaccination has been developed. The most important vaccines are tetanus, diphtheria, poliovirus and *Haemophilus influenzae*. Most killed vaccines are safe but, vaccination with live-attenuated vaccines is generally contraindicated until about 18 months post HSCT and should be avoided in patients with chronic GvHD and those receiving immunosuppressive therapy[20]. Revaccination is recommended at approximately 12 to 18 months post HSCT, but this needs to be individualized. Vaccination earlier than this timeline may not result in an appropriate immune response[20].

GvHD

GvHD occurs when transplanted donor T-lymphocytes react to foreign host cells and it causes a wide variety of host tissue injuries[21]. It can occur despite aggressive immunosuppressive prophylaxis even when the donor is a perfectly matched

Table I: HSCT indications in adult patients

Disease	Status	Allogeneic (Sibling)	Allogeneic (Unrelated)	Autologous
AML	CR1 low risk	CO	NR	CO
	CR1 intermediate risk	S	CO	CO
	CR1 high risk	S	CO	CO
	CR2	S	S	NR
	Refractory	CO	CO	NR
APML	CR1 molecular +ve	S	CO	NR
	CR2 molecular -ve	S	CO	S
ALL	CR1 low risk	CO	NR	NR
	CR1 high risk	S	S	NR
	CR2	S	S	NR
	Refractory	CO	CO	NR
CML	CP1	S #	CO	NR
	AP or CP2	S	S	NR
	BP	NR	NR	NR
MDS	IPSS low	CO	CO	NR
	IPSS intermediate	S	CO	CO
	IPSS high	S	CO	NR
CLL		CO	CO	CO
DLBCL	CR1 high IPI	NR	NR	CO
	CR2	CO	NR	S
	Refractory	CO	CO	NR
Follicular lymphoma	CR1	NR	NR	CO
	CR2	CO	CO	S
	Refractory	CO	CO	CO
Hodgkin lymphoma	CR1	NR	NR	CO
	CR2	CO	NR	S
	Refractory	CO	CO	CO
Myeloma		CO	CO	S
Renal cell carcinoma	metastatic	D	NR	NR
Ovarian carcinoma, small cell lung carcinoma		NR	NR	D
Severe aplastic anaemia		S	CO	NR
SLE & immune cytopaenias		D	NR	CO

(Adapted with modification from ref. [1]).
S—indicated and considered as standard of care in the suitable candidate with access to facilities
CO- clinical option, discussion between the attending physician, patient and an independent physician* with careful consideration of the benefits versus risks is recommended
NR- not recommended
D- developmental, shall be conducted in well-designed clinical trials with ethics review and approval
*clinician with experience in the related clinical condition
In general, HSCT is indicated in adult patients with chronic phase CML in whom treatment with tyrosine kinase inhibitors has failed.

AML-acute myeloid leukaemia; APML-acute promyelocytic leukaemia; ALL-acute lymphoblastic leukaemia; CML-chronic myeloid leukaemia; MDS-myelodysplastic syndrome; CLL-chronic lymphocytic leukaemia; DLBCL-diffuse large B cell non Hodgkin lymphoma; SLE-systemic lupus erythematosus; CR-complete remission; CP-chronic phase; AP-accelerated phase; BP-blast transformation phase; IPSS-International Prognostication Scoring System; IPI-International Prognostic Index

Table II: Cellular and clinical characteristics for various sources of stem cells

Characteristics	Bone marrow	Peripheral blood	Cord blood
1. Stem-cell content	Adequate	Good	Low
2. Progenitor-cell content	Adequate	High	Low
3. T-cell content	Low	High	Low, less mature T-cells
4. Risk of tumour contamination	High	Low	Not applicable
5. HLA matching	Requires close matching	Requires close matching	Less restrictive
6. Engraftment*	Faster than CB but slower than PB	Fastest	Slowest
7. Risk of acute GvHD	Same as PB	Same as BM	Lowest
8. Risk of chronic GvHD	Lower than PB	Highest	Lowest

(Adapted with modifications from ref. [23]).

*Engraftment for adults and children is defined as the point at which a patient can maintain a sustained absolute neutrophil count (ANC) of more than 0.5 x 10^9/L and sustained platelet count of more than 20 x 10^9/L, lasting for more than 3 consecutive days without transfusions.

Table III: Advantages and disadvantages of autologous and allogeneic HSCT

	Autologous	Allogeneic
Advantages	• Safer than allogeneic HSCT • Less transplant related mortality • Does not require immunosuppression • No risk of GvHD or graft rejection • Less infection, especially post engraftment period	• Lower risk of disease relapse or progression • No risk of graft contamination by tumour cells
Disadvantages	• No graft-versus-tumour effect, hence higher risk of disease relapse/progression than allogeneic HSCT • Impaired ability to collect HSC if patient is heavily treated with prior chemotherapy • Graft may be contaminated with tumour cells	• Limited to younger and patients with good performance status • Requires matched donor • Requires immunosuppressive agents and strict monitoring • Higher transplant-related mortality rates • Longer time to recover immune function, higher risk of infection • Risk of GvHD

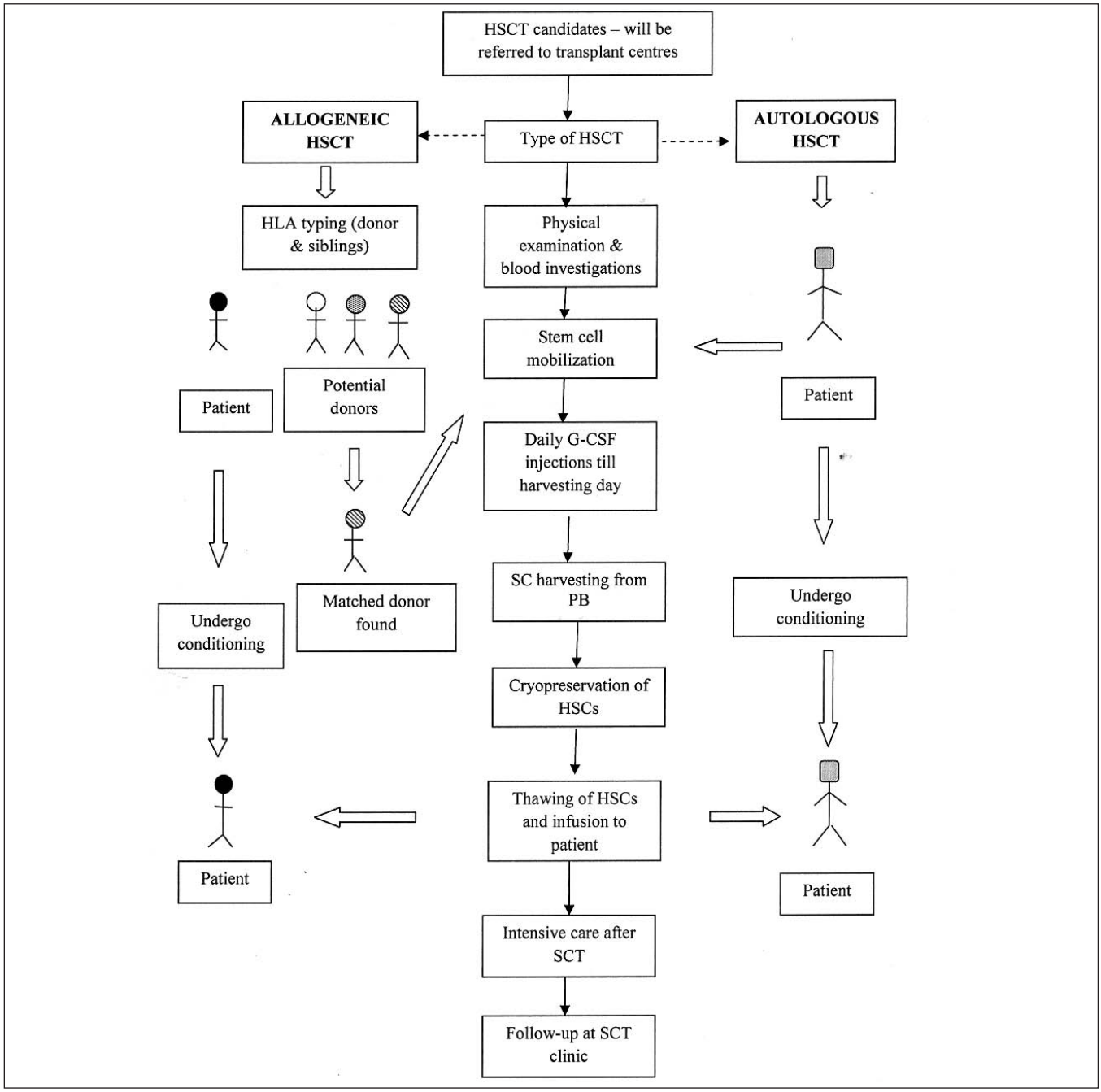

Fig. 1: Process of peripheral blood stem cell transplantation (PBSCT)

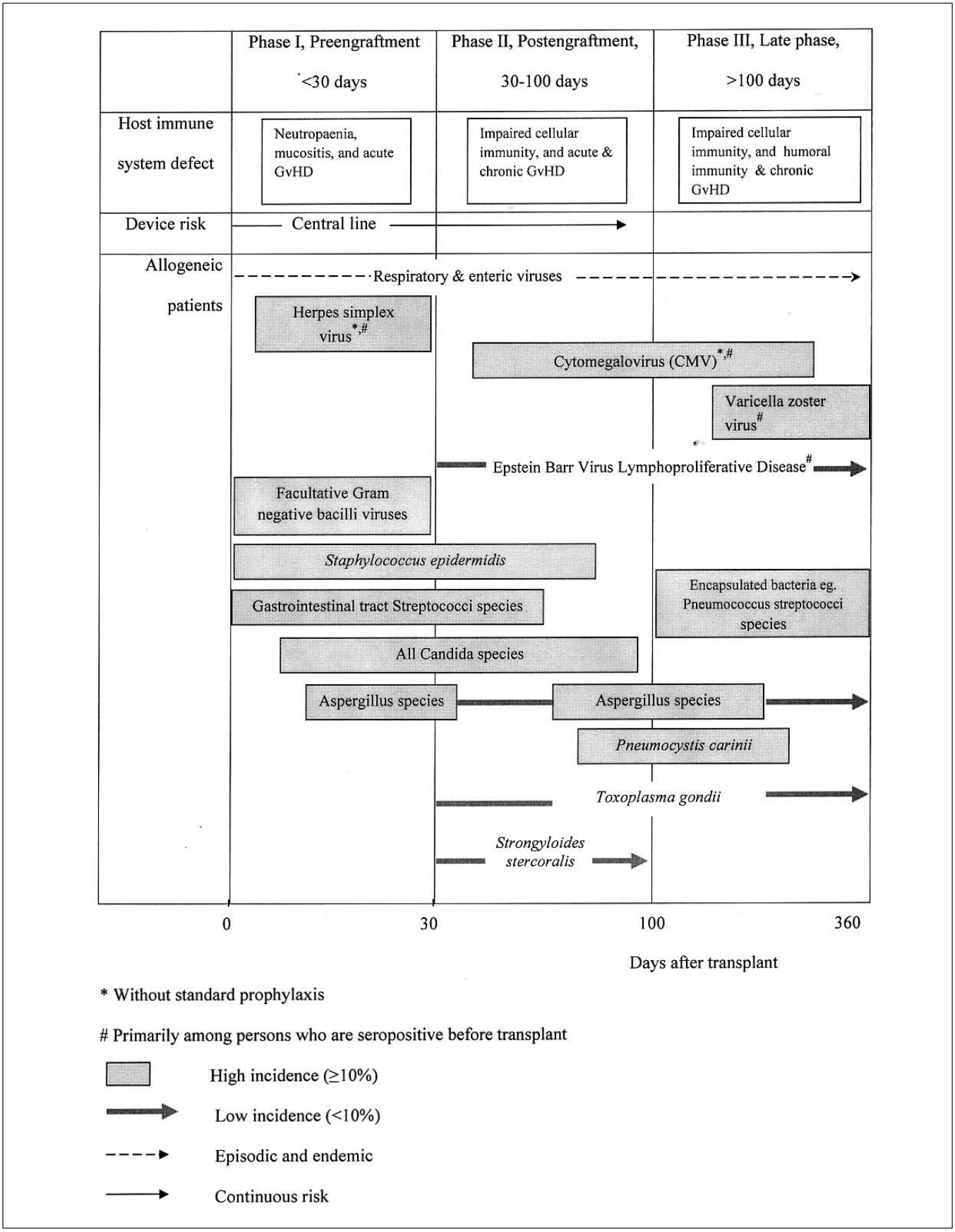

Fig. 2: Phases of opportunistic infection among HSCT recipients

(HLA-identical) sibling. The classification of GvHD is now based upon the clinical manifestations that will determine whether the clinical syndrome of GvHD is acute or chronic, rather than the time to symptomatic onset after HSCT [22].

Acute GvHD comprises classic acute GvHD (arising less than day 100 post HSCT), and persistent, recurrent and late-onset acute GvHD (after day 100)[22]. Incidence of grades II to IV acute GvHD is approximately 10-64% in allogeneic PBSCT patients[9]. HLA mismatch between donor and recipient is one of the major risk factors for acute GvHD[8]. Other risk factors include gender mismatch, older age of the recipient, high dose conditioning regimens, seropositivity to several herpes viruses in the recipient and donor and the graft type[8]. The main target organs involved in acute GvHD are the skin, liver and gut. Preventive and therapeutic measures include immunosuppression with cyclosporine, corticosteroids, tacrolimus, methotrexate and mycophenolate mofetil. Many centres treat mild GVHD of the skin (grade I) with topical steroids alone, but for more severe disease and any degree of visceral GVHD involvement high-dose systemic steroids are usually initiated[22]. The outcome of acute GvHD depends on the grade and the response to treatment. The mortality rate of severe (grade III/IV) or steroid refractory acute GVHD exceeds 60-70%[21].

The incidence of chronic GvHD varies according to studies and can be as high as 85%[9]. The most important risk factor is previous acute GvHD[21]. It can be divided into classic chronic GvHD and overlap syndrome[22]. Skin is usually involved in the form that resembles systemic autoimmune disease such as sclerodermatous and lichenoid skin changes. Xerostoma, keratoconjunctivitis sicca and bronchiolitis obliterans may also develop[21]. The pathophysiology of chronic GVHD remains poorly understood and the disease is treated with various immunosuppressive agents[21]. Supportive care is vital and this includes antimicrobial prophylaxis, artificial tears and anti-osteoporosis agents for patients receiving long term steroids.

Relapse Post HSCT

Relapse of the initial disease is the commonest cause of treatment failure after HSCT. Relapse rates are reported between 2-34% depending on the primary diseases[9]. The risks depend on the disease stage at the time of transplant (complete remission is better), and the type of HSCT and conditioning regimen (autologous HSCT and nonmyeloablative conditioning regimen have higher risk of relapse) and the presence of GvHD (GvHD is associated with a lower risk of tumour relapse)[10]. The prognosis of relapse haematological malignancies after HSCT is generally poor. Treatment of tumour relapse include withdrawal of immunosuppressive agents, salvage chemotherapy, radiotherapy, donor lymphocyte infusion and second HSCT. No single method has been proven effective in all patients.

CONCLUSION

HSCT currently offers the only potential cure for a large number of malignant and non malignant haematological disorders. Future research will focus on ways to decrease the transplant related mortality and increase relapse free survival. As the numbers of patients receiving HSCT increases, there is a need for a better understanding of this procedure among the general physicians who may encounter recipients and donors of HSCT in their clinical practice. This is to ensure that HSCT recipients will be referred early to the transplant physicians or centers if they developed complications even long after the procedure.

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MCQ (TRUE,FALSE)

1. The followings are true regarding the different sources of haematopoietic stem cells (HSC):
   a. The median number of $CD34^+$ stem cells is generally higher in a bone marrow graft compared to a G-CSF mobilized peripheral blood graft (TRUE/FALSE)
   b. CB graft contained more mature T cells compared to peripheral blood graft (TRUE/FALSE)
   c. Mobilization of HSC in sufficient number in the peripheral blood of a healthy donor can be achieved by administration of growth factor alone (TRUE/FALSE)
   d. The number of stem cells is the main limiting factor of a cord blood graft (TRUE/FALSE)
   e. The risk of tumor contamination is higher in bone marrow graft compared to G-CSF mobilized peripheral blood graft (TRUE/FALSE)

2. The following are true regarding haematopoietic stem cell transplantation (HSCT):
   a. Allogeneic HSCT is the treatment of choice in all adult patients with newly diagnosed chronic phase chronic myeloid leukaemia (TRUE/FALSE)
   b. Autologous HSCT is the standard therapy for relapse diffuse large B cell non-Hodgkin lymphoma (TRUE/FALSE)
   c. The incidence of chronic GvHD is higher in peripheral blood stem cell transplantation (PBSCT) compared to bone marrow transplantation (BMT) (TRUE/FALSE)
   d. Cord blood transplantation allows partial HLA mismatches (TRUE/FALSE)
   e. BMT is associated with faster engraftment compared to PBSCT (TRUE/FALSE)

3. The following are true regarding HSCT for patients with acute leukaemias:
   a. Allogeneic HSCT is the treatment of choice for all patients with high-risk acute lymphoblastic leukaemia in CR1 (TRUE/FALSE)
   b. The risk of relapse is associated with the disease state at transplantation (TRUE/FALSE)
   c. Allogeneic HSCT is the standard treatment for acute promyelocytic leukaemia in first complete remission (TRUE/FALSE)
   d. Autologous HSCT is recommended for patients with high risk acute myeloid leukaemia (AML) without a HLA-matched sibling donor (TRUE/FALSE)
   e. Non myeloablative regimen is the preferred conditioning regimen for adult patients with co-morbidities (TRUE/FALSE)

4. Early complications (within 30 days) of HSCT include:
   a. haemorrhagic cystitis. (TRUE/FALSE)
   b. *pneumocystis carinii* pneumonia. (TRUE/FALSE)
   c. veno-occlusive disease. (TRUE/FALSE)
   d. invasive aspergillosis. (TRUE/FALSE)
   e. post-transplant lymphoproliferative disease. (TRUE/FALSE)

5. The following are true regarding graft versus host disease (GvHD):
   a. The risk of acute GvHD increases with multiparous female donor (TRUE/FALSE)
   b. Skin rash of acute GvHD typically spares the palms and soles (TRUE/FALSE)
   c. Methylprednisolone is the first line treatment of acute GvHD (TRUE/FALSE)
   d. Chronic GvHD has features resembling autoimmune disorders (TRUE/FALSE)
   e. Chronic GvHD is associated with an increased risk of relapse of leukaemia (TRUE/FALSE)