Principles of Conditioning Therapy and Cell Infusion

6

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Abstract

Prior to haematopoietic stem cell transplant (HSCT), conditioning therapy is used for disease eradication, creation of space for engraftment and immunosuppression. Conditioning therapy includes combinations of chemotherapy, radiotherapy and/or immunotherapy and can be administered in the immediate days leading up to, and sometimes the days immediately following, the cell infusion. Total body irradiation (TBI) is generally used as part of conditioning regimens preceding allogeneic HSCT and is able to target sanctuary sites where some drugs cannot reach. Cancer immunotherapy treatment harnesses the body's natural defences to fight the cancer, by involving components of the immune system. Conditioning therapy can have acute and chronic side effects which vary depending on the intensity of the treatement. Nursing implications include patient education and information, toxicity assessments, close monitoring and protocolised, evidence-based action plans. Stem cell infusion is usually a safe procedure but can cause adverse reactions ranging from flushing and nausea to life-threatening anaphylaxis. There should be written policies for the administration of cellular therapy products, and nurses must have comleted training and achieved competency in order to safely administer haematopoietic stem cells.

Keywords

Haematopoietic stem cell transplant · HSCT · Conditioning therapy · Chemotherapy · Total body irradiation · TBI · Immunotherapy · Stem cell infusion

6.1 Conditioning

Conditioning therapy in haematopoietic stem cell transplant (HSCT) is central to the preparation or 'conditioning' of the patient for the transplant. The three main goals of conditioning therapy are:

1. Eradication of disease
2. Creation of 'space' in the bone marrow for donor stem cells to engraft
3. Immunosuppression to decrease the risk of rejection of the donor cells by the host cells

Conditioning therapies include combinations of chemotherapy, radiotherapy and/or immunotherapy, to create different regimes. The aim of conditioning regimens is to reduce relapse and

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M. Kenyon, A. Babic (eds.), *The European Blood and Marrow Transplantation Textbook for Nurses*,
https://doi.org/10.1007/978-3-031-23394-4_6

Table 6.1 Examples of myeloablative, non-myeloablative and reduced intensity regimens

Myeloablative	Non-myeloablative	Reduced intensity
Bu/Cy/Mel (busulfan, cyclophosphamide, melphalan)	Flu/Cy/ATG (fludarabine, cyclophosphamide, ATG)	Flu/Bu (fludarabine, busulfan)
TBI/TT/Cy (TBI, thiotepa, cyclophosphamide)	Flu/TBI (fludarabine, TBI)	Flu/Mel (fludarabine, melphalan)
Cy/VP/TBI (cytarabine, etoposide, TBI)	TLI/ATG (total lymphoid irradiation, ATG)	Flu/Cy (fludarabine, cytarabine)

Adapted from EBMT (2021)

rejection and can be adjusted to reduce treatment-related toxicity. The constituents, administration days and doses can depend on the disease and type of transplant donor. Other factors to consider when deciding the optimal conditioning regime are patient age, comorbidities and prior treatment potentially influencing toxicity risk. Myeloablative (MA) conditioning regimes are the most intense and most toxic, and while still widely used, we now also have the availability of non-myeloablative (non-MA) and reduced intensity conditioning (RIC) regimes. These are less toxic and so better designed for those who would not tolerate or do not require MA regimens. Additionally, the ongoing appraisal and investigation of conditioning chemotherapy approaches has supported the establishment of post-transplant Cyclocophosphamide as a vehicle to promote engraftment in haplo-identical related donor transplants without the extensive GvHD previously associated with the haplo approach (Luznik et al. 2008).

Table 6.1 provides examples of some more commonly used regimes adapted from the EBMT Handbook (Carreras et al. 2019)

6.2 Chemotherapy

Dividing cells such as bone marrow stem cells proliferate and replicate in order to retain their function. Cytotoxic chemotherapy works by destroying rapidly dividing cells, including malignant cells. This is done by preventing the cells from dividing or by causing cell death (apoptosis) during different phases of the cell cycle.

The cell cycle comprises of five phases:

1. G0 phase—This is the resting phase which can last for months.
2. G1 phase—This is the growth phase, where RNA and protein synthesis occurs.
3. S phase—DNA is replicated so that when the cell divides, the new cell will have a copy of the genetic information. This phase lasts from 18 to 20 h.
4. G2 phase—Further protein synthesis occurs preparing the cell for mitosis; this phase lasts from 2 to 10 h.
5. M phase—The cell splits into two new cells. This phase lasts about 30–60 min.

There are three different means of classifying chemotherapy drugs: according to their cell cycle activity, their chemical groups or their mode of action. This chapter focuses on the mode of action classification, which is summarised in the table below 6.2.

6.2.1 Combination Chemotherapy

As previously mentioned all cells go through five phases during the cell cycle. Certain cytotoxic chemotherapy drugs work only at a specific phase of the cycle, whilst other drugs are not phase specific. In cytotoxic drug combinations such as those used in pre-BMT conditioning, it is logical to attack multiple phases of the cell replication cycle to prevent mutation and resistance from occurring. Combination chemotherapy allows for maximum cell kill, as each drug targets cells independently at different stages of the cell cycle.

Table 6.2 Drugs commonly used in conditioning regimes

Cytotoxic classification	Mode of action	Examples
Alkylating agents	They prevent replication by substituting alkyl groups for hydrogen atoms in cells. This inhibits DNA replication and transcription	Melphalan Iphosphomide Busulfan
Antimetabolites	These agents disrupt cellular metabolism resulting in disrupted DNA and apoptosis. Act in the S phase of the cell cycle	Methotrexate Cytarabine Fludarabine
Antimicrotubular agents	They inhibit RNA and DNA synthesis and inhibit DNA repair resulting in blockade of DNA and RNA synthesis	Daunorubicin Doxorubicin
Epipodophyllotoxins	These agents are derived from the root of the mandrake plant and act in the G2 and S phase interfering with topoisomerase II enzyme reaction	Etoposide
Vinca alkaloids	These are extracts from the pink periwinkle plant. They bind to microtubular proteins causing apoptosis acting mainly in the M phase	Vincristine Vinblastine

Adapted from Amjad et al. (2022)

If the toxicities of the chemotherapy drugs when used in are not amplified, the optimal dose can be administered without the high-grade toxicities. Therefore, the deployment of combination chemotherapy agents with different mechanisms of action and also nonoverlapping toxicities can be chosen to decrease resistance and toxicities (Amjad et al. 2022)

In order to understand the principles of conditioning chemotherapy, it is important to appreciate approaches to chemotherapy administration and the role they have in achieving the intended outcomes.

6.2.2 Cycles and Scheduling

Chemotherapy is administered in cycles according to a schedule, in order to allow for recovery of the bone marrow and immune system after administration (Brown and Cutler 2012; Grundy 2006). Malignant cells are expected to have a lengthier time to recover than normal cells. In this way, by scheduling the treatment, 'normal' cells can recover from toxicity, whilst the malignant cells will be reduced with continued cycles of treatment. Administration of chemotherapy in cycles allows for the possibility of a larger dose of drugs to be given over a short period of time.

In leukaemia and lymphoma treatment, chemotherapy is usually divided into different phases:

- Induction: The first aim of the treatment is to achieve remission. Chemotherapy is administered in order to eradicate the malignant cells.
- Consolidation (intensification): After remission is achieved, further treatment is given in order to prevent a recurrence of malignant cells. Consolidation chemotherapy can include radiotherapy or a stem cell transplant.
- Maintenance: Treatment is given in order to 'maintain' remission and prevent relapse. Maintenance treatment may include chemotherapy, hormone therapy or targeted therapy.

6.2.3 Modes of Administration

Cytotoxic therapy can be delivered via different routes. The four most used in HSCT are:

1. *Intravenous* (*IV*): This is the most common route of administration in HSCT. The drug is delivered directly into the blood stream via a cannula or a central venous access device. Risks to IV administration include extravasation and chemical phlebitis (chemical reaction to the vein causing hardening of the view or cording).
2. *Subcutaneous*: This is administered as an injection under the skin. Risks include irritation to the surrounding tissue, trauma (which could be due to low platelet count) or infection.

3. *Oral:* This route is usually self-administered. It is important that the patient is able to swallow, has sufficient manual dexterity and is compliant. Risks including vomiting after a given dose can reduce bioavailability.
4. *Intrathecal* (*IT*): This is administration by lumbar puncture into the cerebrospinal fluid to treat or prevent disease in the central nervous system (CNS). Intrathecal administration can be fatal if the incorrect type of cytotoxic agent is used, i.e. vinca alkaloids. National guidance has been publicised for the safe administration of IT chemotherapy.

6.2.4 Side Effects and Nursing Implications

- Chemotherapy side effects can be acute or chronic.
- Chemotherapy destroys not only malignant cells but also rapidly dividing 'normal' cells. The 'normal' cells that are most frequently affected include bone marrow cells, hair follicles, mucosal lining of the GI tract and skin, fertility and germinal cells.
- Nursing implications involve patient education and information, toxicity assessments, close monitoring and action plans.
- Chapters 10 and 11 discuss acute complications and supportive care in more detail.

6.3 Radiotherapy

Radiotherapy in HSCT is used as part of lymphoma treatment, as prophylaxis and treatment of disease and as palliative treatment for myeloma and lymphoma. Radiotherapy uses ionising radiation to control or kill malignant cells.

6.3.1 Total Body Irradiation

Total body irradiation (TBI) alongside high-dose chemotherapy helps to kill off leukaemia, lymphoma or myeloma cells in the bone marrow. This allows the patient to be in a preparation phase to receive the donor stem cells as part of the recovery stage of the treatment.

TBI is widely used as part of myeloablative, reduced intensity and non-myeloablative conditioning regimens preceding HSCT. As well as eradicating disease, immunosuppressive effect and creating space for donor cells to engraft; TBI is able to target sanctuary sites such as the CNS or gonads where some drugs cannot reach.

Most centres use a linear accelerator machine as a source of radiation. Patients are positioned either on their side or in a lateral position at a calculated distance from the machine. TBI is delivered in various doses and scheduling. The dose can be single (1–8 Gy total dose), fractionated (10–14 Gy total dose over 3 days) or hyperfractionated (14–15 Gy total dose over 4 days). As with chemotherapy scheduling, fractionated doses of TBI minimise toxicity (Carreras et al. 2019).

Some centres use lead shielding blocks to protect parts of the body such as the lungs and eyes; however, shielding organs could potentially shield leukaemic cells, so many centres opt not to do this.

6.3.2 Side Effects and Nursing Implications

Side effects of TBI can be acute or chronic. As TBI is usually given in combination with chemotherapy, it can be difficult to differentiate between the causes of the toxicities. Immediate side effects of TBI include bone marrow suppression, alopecia, nausea, vomiting, parotid swelling and erythema.

Chronic side effects of TBI include cataracts, infertility and interstitial pneumonitis. Nursing implications involve patient education and information, toxicity assessments, close monitoring and action plans (Carreras et al. 2019).

Chapters 9 and 10 discuss acute complications and supportive care in more detail.

6.4 Monoclonal Antibodies in Conditioning Therapy

There are two main agents that may be used to target T-cells prior to cell infusion to support engraftment and reduce risk of GvHD.

Alemtuzumab, otherwise called CAMPATH-1H, is a humanized monoclonal antibody directed against the CD52 antigen of lymphocytes (T-cells) for depletion of donor and recipient T-cells to prevent graft-versus-host disease and graft rejection.

Anti-thymocyte Globulin (ATG) is an important in vivo T-cell depletion strategy, which reduces the risk of graft-versus-host disease in HLA-matched or -mismatched donor allografting.

However, while these approaches effectively target alloreactive T cells, this is at the expense of potentially increasing the risk of post-haematopoietic cell transplantation infections and delayed immune reconstitution (Nishihori et al. 2016).

6.5 Paediatric Considerations

6.5.1 Conditioning

There are differences between adult and paediatric patients' conditioning. Children can generally tolerate side effects better than adults, and higher doses may be used. On the other hand, conditioning regimens affect growth and endocrine development of the child.

Studies so far indicate that reduced intensity conditioning (RIC) in haematopoietic cell transplantation may have an important role in treating children with primary immune deficiencies: such regimens can be used without severe toxicity in patients with pre-transplant infections or severe pulmonary or hepatic disease. RIC has become a standard of care and has extended the offer of allogeneic transplantation to many patients who were previously considered ineligible for this procedure (Chiesa and Veys 2014).

Disease-specific treatment protocols are described in the EBMT Handbook (Ch 13) (Carreras et al. 2019). Chemotherapy and radiation therapy side effects are discussed in more detail in this textbook in Chap. 8.

6.5.2 Chemotherapy

Children in general tolerate side effects better than adults, so higher total doses may be used (Satwani et al. 2008).

When treating paediatric patients, prescriptions should be made by body surface area (BSA) mg/m^2 or mg/kg using *recent weight and height*.

6.5.3 Total Body Irradiation

TBI has severe side effects when administered to children and adolescents, and it should be avoided, whenever possible. The risk for secondary malignancies is significantly higher compared to pharmacological conditioning. Most teams use conditioning regimens that do not involve TBI (Carreras et al. 2019).

When TBI is used, it is commonly given in fractions (two doses per day) to minimise the side effects.

Paediatric patients need age-appropriate preparation for radiotherapy. This can be done by a play therapist, but if there is no such professional, it should be done by a nurse. Preparations should be started well in advance where possible to allow the patient and parents ask questions. Children may choose to listen to music or fairy tales whilst having TBI. Immobilisation is a prerequisite for accurate radiotherapy, so anaesthesia is required for younger children.

6.6 Cell Infusion

Cell infusion processes and procedures are largely the same for adults and paediatrics and are discussed together in this chapter.

Haematopoietic stem cells (HSCs) can be procured from the patient (autologous) or from a donor (allogeneic or cord blood).

HSCs procured from the patient are almost always sourced from peripheral blood during apheresis (see Chap. 5).

HSCs procured from a donor can be sourced from the peripheral blood (apheresis), bone marrow or umbilical cord.

After harvesting, HSCs can be stored using cryopreservation. Dimethyl sulfoxide (DMSO) is a common cryopreservative used in the storage of HSCs.

Documented confirmation of HSCT donor fitness or available cell therapy product is required prior to commencing conditioning therapy to ensure that conditioning therapy is followed by the timely infusion of the intended cellular product. The only exception to this is donor lymphocyte infusion, although confirmed dates of donation and available product are still of course necessary to planning the patient infusion. There are a number of basic principles to follow for safe infusion that are outlined in this section. However, each centre has its own specific Standard Operating Procedure (SOP) which must be referred to for local guidance.

The two main product categories are fresh or cryopreserved with different considerations for each.

There are minimum documentation requirements. These should be signed and with copies filed or scanned to the patient record:

- Prescription: The cell product prescription will specify the number of bags to be infused
- Cell infusion record: Each product infusion must be documented on a cell infusion record or worksheet with cell product information, infusion duration of each bag or unit and any infusion issues at the bedside or side effects observed by the registered nurse.

Prior to commencing the cell infusion there are a number of preparation steps at the patient bedside. The following list is an example of the equipment needed, and each centre will have its own checklist to ensure the correct preparation has taken place.

Equipment

Automatic blood pressure cuff	250mL bag of normal saline (500mL bag if patient is to receive more than 5 bags of the product)
O2 saturation monitor	Blood product infusion Y- tubing with 170 micron filter
O2 and nasal prongs	Emergency trolley with crash medications

Example of procedures between transplant unit nursing team and stem cell laboratory

PROCEDURE for Patient Preparation by Registered Nurse

- On the day of cell infusion, contact stem cell laboratory should confirm cell infusion time (this may be dependent on chemotherapy excretion or cell arrival if fresh unrelated donor cell infusion)
- Administer the pre-medications as per protocol orders
- Prime giving set and filters with normal saline attached to one Y-extension, and attach tubing to the large lumen of patient's Central Venous Catheter Access Device. (CVAD)
- Record baseline oxygen saturation, pulse, blood pressure and temperature
- Once the product arrives on unit, a certified registered nurse checks the infusion record or worksheet accompanying cells to verify the patient information, with the patient notes, the patient and the patient armband

PROCEDURE for Preparation by Stem Cell Laboratory Technician

- Set up dry shipper and water bath outside patient's room.
- Stem cell technician verifies the cell therapy product with the nurse or physician

Infusion: Key Points

For cryopreserved products, thaw one bag at a time

Upon completion of thawing perform visual inspection of bag and contents

Infuse cells quickly after thawing to optimise viability, documenting infusion start and finish time for each bag on the cell infusion record aiming to complete each bag in <10 min

Monitor vital signs throughout the cell infusion and continue to monitor once complete

6.6.1 Adverse Reactions

An adverse reaction is defined as a noxious and unintended response suspected or demonstrated to be caused by the collection or administration of a cellular therapy product or by the product itself (EBMT 2021).

The stem cell infusion is a generally safe procedure, but it can cause a variety of adverse reactions ranging from flushing and nausea to life-threatening reactions. It is imperative that the healthcare team is trained for early identification and managing of possible adverse reactions. Nurses must obtain baseline vital signs including temperature, breath sounds, pulse oximetry, weight and fluid status prior to and during the cell infusion.

Possible adverse reactions associated with stem cell infusion vary according to whether the cells have been cryopreserved or are infused as fresh:

- *Fresh*
  - Allergic reaction
  - Haematolytic transfusion reaction
  - Fluid overload
  - Micropulmonary emboli
  - Infection
- *Preserved*
  - Bad taste in the mouth, nausea and vomiting (DMSO)
  - Arrhythmia hypertension
  - Haemoglobinuria
  - Allergic reaction
  - Haemolytic transfusion reaction
  - Fluid overload
  - Micropulmonary emboli
  - Infection (Costa Bezerra Freire et al. 2014; Tomlinson and Kline 2010; Truong et al. 2016; Vidula et al. 2015)

6.6.2 Nursing Care: Pre-, During and Post Stem Cell Infusion

6.6.2.1 Pre-infusion Assessment

Maintain a Safe Environment

Ensure that your patient is prepared and the room is organised out in a way that you have access to the patient and you have access to everything you need including oxygen and suction. The patient should be nursed on a bed during the stem cell infusion, in case of severe allergic reaction.

Baseline Observations

Record baseline observations in order to assess the patient's physiological status during and post infusion.

Patient Preparation for Infusion

If patients are receiving cells previously cryopreserved with DMSO, they should receive a premedication with antihistamine, antipyretics and anti-emetics. The nurse should discuss the procedure including length of time, how the patient may feel and what to tell the nurse if they experience any of the common side effects. Encourage your patient to tell you how they feel during the entire procedure, to ensure adverse incidents are spotted, to offer reassurance or to ensure side effects are managed.

IV Line Care

Check the IV line for patency. On the whole, patients undertaking a stem cell infusion will have a permanent, central line in situ. Common lines used for this treatment are PICC lines and Hickman lines. Ensure aseptic non-touch technique is used to prevent the risk of infection.

Toileting

Discuss with the patient and encourage toileting prior to starting the procedure in order to minimise interruption to the stem cell infusion and also ensure safety for the patient.

Psychological Support

Day zero can be a momentous occasion for someone who requires a stem cell transplantation. Patients may experience a range of emotions,

from elation through to distress, anxiety, vulnerability and helplessness. Using simple techniques such as discussing the procedure, and listening and offering reassurance may help to reduce patients anxiety.

6.6.2.2 During Stem Cell Infusion

IV Line Care

Ensure aseptic non-touch technique is used to prevent the risk of infection.

Physiological Monitoring

Should be carried out at least every 10–15 min and increased if there are any concerns with the patients' condition during the infusion. O_2 saturations are monitored constantly during infusion. Report and treat problems as they arise (i.e. drop in saturations, give O_2 as prescribed)

Assess for Potential Side Effects

Patients can have mild to severe reactions to a cell infusion. Autologous stem cells tend to be cryopreserved. Patients can experience allergic reactions including nausea, flushing, rash, chest tightness, shortness of breath and chills. For anaphylaxis, follow your centre guidelines for managing an anaphylaxis event. For other side effects, the infusion can be slowed down according to how the patient tolerates the infusion. Reassure the patient and treat the side effects as they occur.

6.6.2.3 Post Stem Cell Infusion

Physiological Monitoring

Assess for later effects of the cell infusion. Observations should be performed half hourly for the next 2 h, then hourly for another 2 h, and four hourly thereafter.

Documentation

In addition to completing the cell infusion record and signing the prescription for cell infusion, the bedside nurse should document the care event in patients' medical records.

6.6.3 JACIE Standards

The JACIE process has been explained in detail in Chap. 1. JACIE Standards give clear and detailed information around safe administration of cell therapy products. Nurses must have training and have achieved competency for administration of cellular therapy products.

Each centre should have written policies addressing safe administration of cellular therapy products. This includes policies for determining the appropriate volume and the appropriate dose of red blood cells, cryoprotectants and other additives as well as for the infusion of ABO-incompatible red blood cells in allogeneic cellular therapy products. Two qualified persons shall verify the identity of the recipient, the product and the order (prescription) for administration (JACIE standards B7.6).

For more detailed information, please visit the www.jacie.org.

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Further Reading

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