CHAPTER 10

Supportive care

Tamás Masszi, Arno Mank

1. Introduction

Supportive care comprises all treatments given to prevent, control, or relieve complications and side effects in the HSCT process. Supportive care in HSCT is essential in optimising the outcome of the treatment. This chapter will focus on protective issues including protective isolation and hygiene aspects, nutritional support including low bacterial diet, the use of central venous devices and their consequences and complications, the use of haematopoietic growth factors, intervention pre- and post-transplant to prevent and treat oral mucositis, and anti-emesis strategies.

2. Protective issues

Patients with haematologic malignancies treated with HSCT are at great risk of developing infective complications because of marked immunosuppression and prolonged pancytopenia, together with mucosal injury. In addition to antimicrobial prophylaxis, there are other important strategies to prevent infections, together building up a network of infection control measures. Key points of these are: protective environment, protective clothing and equipment, hand hygiene, low microbial diet, vaccination and exclusion policy and monitoring infectious complications.

2.1 Protective environment (isolation) and cleaning

A variety of practices exist regarding the use of isolation for immunocompromised patients; however, the effectiveness of protective isolation has not been established. Numerous studies have assessed the effect of laminar airflow or HEPA filtration with conflicting results. Most of these studies tested several interventions simultaneously (e.g., chemoprophylaxis, protective clothing, and sterile food), making it difficult to determine whether independent effects of individual interventions were present. However, it has been shown that there is some protective effect of laminar airflow and HEPA filtration against infections, particularly aspergillosis, especially during hospital building programmes (1). Patient transport to diagnostic facilities or other wards should be avoided if possible or at least time spent outside the protective environment should be minimised. In addition it is important to improve hygiene measures such as daily cleaning and changing of bed linen. Fresh or potted flowers/plants should be banned from the patient's area.

2.2 Personal and hand hygiene, protective clothing and equipment

Because a large proportion of infections in patients with neutropenia is associated with the patient's own microbial flora, the patient's personal hygiene is of

outstanding importance. Hand washing and hand disinfection of nursing and other personnel is also important and has been proven by multiple, well-designed studies to be one of the most effective ways to prevent the transmission of infection. There have also been studies of the benefit of antiseptic baths, but the evidence for an association between antiseptic bathing and reduced risk of infection is contradictory. Although several studies with gowns or other protective clothing have not been shown to reduce the risk of infections it seems to be prudent to discourage visitors from wearing coats or other outerwear in the patient's room.

2.3 Basics of hand hygiene

- This is important for patients as well as staff. All patients should regularly wash their hands with soap and water or use an antiseptic hand rub.
- Personnel should wash hands with soap and water between each patient contact, if hands are visibly dirty or contaminated. The same procedure should be followed if *C. difficile* is present. In all other cases alcohol-based hand rubs alone can be used.
- Hands may remain colonised with microorganisms after hand washing if hands are not dried properly.

2.4 Low bacterial diet

It has been argued that a diet containing food with low levels of bacteria can possibly help to reduce the number and/or severity of infections in cancer patients. However, there is no clear evidence that the use of a low bacterial diet (LBD) actually decreases the number of infections.

It is clear from numerous surveys of current practice that the majority of hospitals place neutropenic patients on a restricted diet. The range and level of restrictions regarding indications for starting and stopping LBD and the specific dietary products allowed showed large variations and contradictions (2). Moreover, compliance with restricted diets is inconsistent. In a randomised clinical trial of 153 patients a low bacterial diet did not prevent major infection or death (3). Other studies on smaller patient populations also failed to find significant difference in the amount of infections with a low bacterial diet compared to a normal diet. In spite of the current routine practice of applying LBD in most transplant wards, the true scientific proof for food restrictions remains lacking.

2.5 Vaccination and exclusion policy

It is advisable that health care workers and visitors in contact with transplant patients should be vaccinated for influenza, especially during the flu season. Personnel should also possess protective titers for *Varicella-zoster virus* (VZV). Individuals showing

signs and symptoms of a respiratory, gastrointestinal or muco-cutaneous infection should be excluded from work or should not be allowed to visit the patient.

2.6 Monitoring infection rate and antimicrobial resistance

Every centre should have a policy for monitoring the incidence of infections. At the same time trends of antimicrobial resistance must carefully be followed. The incidence of invasive fungal infections must be monitored, and a twofold increase within a six month period should prompt examination of possible environmental and logistic factors.

3. Nutritional and metabolic support

Nutritional and metabolic support prevent loss of lean body mass, fluid and electrolyte imbalance, increase patient comfort and improve survival for patients who are unable to eat or absorb nutrients for a prolonged period of time. The goal is to enable the patient to recover the ability to take in and absorb food orally as quickly as possible following transplantation.

3.1 Caloric and metabolic alterations

Most HSCT patients develop significant mucositis and have difficulties in maintaining adequate oral nutrition. Decreased oral intake caused by nausea, vomiting and diarrhoea, decreased nutrient absorption and loss of nutrients from the gut result in a negative nitrogen balance. This is further complicated by the catabolic effects on skeletal muscle exerted by the underlying disease, the conditioning regimen and subsequently by transplant complications such as GvHD and sepsis.

3.2 Nutritional support

Impaired nutritional status before transplantation is a negative prognostic factor for outcome after HSCT and better nourished patients have a shorter time to engraftment. Irrespective of nutritional status, however, parenteral nutritional support is commonly administered prophylactically after HSCT until patients are able to maintain an adequate oral nutritional intake, usually following bone marrow recovery. Although hypothetically enteral nutrition is possible, total parenteral nutrition (TPN) is largely favoured in HSCT patients because nausea, vomiting and oro-oesophageal mucositis prevent the insertion and subsequent tolerability of nasogastric tubes. Moreover, virtually all patients undergoing HSCT have a central venous catheter in situ through which TPN can be easily administered. Finally, parenteral nutrition probably allows better modulation of fluid, electrolyte, and nutrient administration which can be of critical importance when complications such as GvHD or VOD arise.

3.3 Total parenteral nutrition

The routine use of TPN during transplantation is based on a study that randomly assigned 137 previously well nourished patients undergoing BMT to either prophylactic TPN or intravenous maintenance fluids (dextrose, electrolytes, minerals, trace elements and vitamins). Treatment started during conditioning, and continued for 4 weeks following transplantation. Compared to the control arm, patients receiving TPN had significantly better overall and disease-free survival, and a longer time to relapse. Notably, 61% of control patients eventually required TPN because of a decline in their nutritional status (4). In contrast, other studies have not provided strong support for the routine use of TPN in patients with HSCT. However, the care of recipients of HSCT has changed significantly over the last twenty years, e.g. hospital stays are shorter due to the increasing use of peripheral blood stem cell transplantation and the use of recombinant haematopoietic growth factors, and a number of questions remain unanswered regarding nutritional support. For instance in a prospective randomised trial, 57 patients undergoing BMT received either prophylactic TPN or an enteral feeding programme. TPN was associated with significantly more days of diuretic use, more frequent hyperglycaemia and more catheter-related complications. Although the patient cohort was small this study suggests that the role of TPN in patients undergoing HSCT deserves further investigation (5). In a double blind study, 258 patients were randomly assigned to receive either TPN or hydration in an outpatient setting. Patients who received TPN had a delay in the resumption of 85% of their caloric requirement (16 versus 10 days), suggesting that the administration of TPN may suppress normal appetite (6). Another study attempted to define subgroups of patients who were likely to require TPN, using the following three criteria to define the need for TPN: severe malnutrition at admission, a prolonged (at least 7–10 days) period of minimal oral intake and clinical weight loss exceeding 10% during treatment. TPN was found to be necessary in only 55% of patients undergoing HSCT, with a range of 37% for autologous recipients to 92% for those receiving an HLA mismatched allograft (7).

According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline (2009), parenteral nutrition (PN) in HSCT patients should be reserved for those with severe mucositis, ileus, or intractable vomiting. PN should start either when oral feeding falls below 60–70% of requirements for three days or may be started on the day following stem cell infusion if the patient is malnourished and it should be generally maintained for 15–20 days (8).

3.4 Caloric, protein and other necessities

Energy requirements in HSCT patients may exceed 130–150% of the estimated basal energy expenditure. Protein needs are also elevated. The recommended amino acid

dose in TPN is 1.5–2 g/kg/day. A balanced caloric intake with both fat and carbohydrate is recommended. Long chain triglycerides (LCT), containing saturated, fatty acid moieties of 20-24 carbons or a mixture of long chain and medium chain triglycerides (MCT, 6-12 carbons) should provide 30% of caloric intake. MCT seem to be advantageous in TPN over LCT because they are more water soluble, more rapidly cleared from plasma, have protein sparing effects and do not accumulate in the liver or adipose tissue. Clinical studies have suggested that mixtures of MCT and LCT are advantageous in patients with respiratory illnesses, hepatic dysfunction, and sepsis with multi-system organ failure compared to LCT alone. Electrolytes, minerals, vitamins and trace elements (chromium, zinc, copper, manganese, selenium) are added to the TPN according to the recommended daily amount.

Glutamine supplementation of TPN has been addressed recently as glutamine is an important precursor for nucleotide synthesis and thus can be a source for rapidly dividing cells, such as gastrointestinal epithelial cells. Although several studies have evaluated the effect of enteral or parenteral administration of glutamine on gastrointestinal toxicity, none have shown a clear preventative or curative effect on intestinal mucositis. On the other hand, prospective studies have suggested positive effects of glutamine administration after HSCT on nitrogen balance, infectious complications and length of hospital stay (9). Preliminary data support the concept that parenteral glutamine may preserve hepatic function in HSCT recipients by maintaining hepatic glutathione concentrations which in turn protects hepatocytes from the oxidant stress of the conditioning regimen. Glutamine supplementation may also have a role in preventing and possibly treating VOD. A meta-analysis of 29 studies confirmed some beneficial effects of adding glutamine to parenteral nutrition in HSCT recipients (10).

3.5 Evaluation of nutritional status and monitoring nutritional support

Nitrogen balance is considered the most accurate way of assessing nutritional status in HSCT recipients as it is the direct expression of the imbalance existing between protein breakdown and synthesis. From studies published of TPN in HSCT some kind of consensus can be derived concerning nutritional status/support monitoring parameters. Daily monitoring of weight (primarily to judge hydration status) is essential, together with electrolytes, BUN, creatinine, and glucose. Liver function tests, serum albumin, transferrin, triglyceride and nitrogen balance are also helpful (Table 1).

3.6 Timing of nutritional support

The current practice of the timing of TPN is heterogeneous. In the study of Weisdorf (which became the scientific basis of routine administration of TPN in HSCT

Table 1: **Monitoring of nutritional support during the in-patient stay**

Daily	Two times a week	Once a week
- weight (fluid balance) - blood glucose - serum electrolytes - BUN - serum creatinine - calorie and protein intake	- liver function tests - serum calcium - serum magnesium - serum phosphorus	- nitrogen balance - serum transferrin - serum albumin - serum triglyceride - serum zinc

patients), parenteral nutrition was started before the conditioning regimen and continued to day 28 following HSCT. However, in many centres TPN is started only when severe mucositis develops. Others initiate TPN on day 1 post-transplant and continue for 2–3 weeks according to the intensity and duration of mucositis. TPN is usually not administered routinely to recipients of autologous transplantation unless prolonged mucositis occurs.

3.7 Complications of TPN

Complications essentially can be divided into two types: those related to the central venous catheter, and metabolic complications.

3.7.1 Metabolic complications

The most remarkable metabolic complications are hepatic enzyme elevations. The initial manifestation is usually an elevation of transaminases 1–2 weeks after the start of TPN. Increases in serum bilirubin and alkaline phosphatase generally occur 1 or 2 weeks later. These changes often resolve spontaneously without long-term consequences especially if the period of administration of TPN is short (not longer than 3 months). However elevated liver enzymes have multiple causes in HSCT patients and the differential diagnosis may be difficult. Drug toxicity, infections, GvHD, VOD, or recurrence of the original malignancy should also be considered (Table 2). If all

Table 2: **Common causes of elevated liver enzymes in the post-transplant period**

- Side effects of drugs (methotrexate, cyclosporin-A)
- Infections (bacterial, fungal, viral)
- Veno-occlusive disease of the liver
- Graft versus host disease
- Relapse of malignancy
- Parenteral nutrition

these possible causes are excluded various other measures can be initiated e.g. shortening the period of infusion of TPN from 24 hours to 12–20 hours, introducing some oral feeding, decreasing the non-protein caloric intake and commencing treatment with ursodeoxycholic acid (Table 3).

Table 3: **Treatment approach to elevated liver enzymes during TPN**

- Search for causes other than TPN (see Table 2)
- Shorten TPN cycle to 12-20 from 24 hours/day
- Reduce the non-protein caloric intake by 10-15% of the total daily calories
- Initiate some oral intake if possible
- Treat with ursodeoxycholic acid
- Utilise oral metronidazole to decrease enteral endotoxin formation

3.8 Diet in graft versus host disease of the gut

Patients suffering from intestinal graft versus host disease may benefit from glutamine-supplemented PN. The optimal dose of glutamine is not established but studies have suggested around 0.6 g/kg/day.

The oral diet should be adjusted to the severity of GvHD in general: avoid fat, fibre and lactose.

A 4-step schedule is recommended:

Step 1 - bowel rest; glutamine-supplemented PN

Step 2 - liquid oral diet

Step 3 - solid food; lactose-free, low fibre, fat reduced

Step 4 - slowly increase the amount of solid foods. Lactose-containing products are often the last to be tolerated (11).

3.9 Conclusions

Nutritional support is an integral part of the supportive care of patients receiving HSCT and the main tool remains TPN. It seems to be prudent to administer TPN to patients undergoing HSCT if they have severe mucositis or gastrointestinal manifestations of GvHD, when a long period of insufficient oral intake is anticipated. The most common complications of TPN are central venous catheter related.

4. Central venous devices

Health-care institutions purchase millions of intravascular catheters each year. Central venous catheters (CVC) are the devices most frequently used for vascular access in HSCT. Although CVC are indispensable in HSCT, they also represent a significant source of complications including catheter-related bloodstream infections, complications of

insertion, venous thromboembolism, mechanical obstruction, dislodgment and leakage. The most important of these complications are bloodstream infections with an estimated incidence of 5/1000 patient days and a mortality rate between 3–25%.

4.1 Catheter related blood stream infection

Catheter related blood stream infection (CRBSI), is defined as bacteraemia or fungaemia in a patient with an intravascular catheter with more than one positive blood culture obtained from a peripheral vein, clinical manifestation of infections (i.e. fever, chills, and/or hypotension) and no apparent source of the blood stream infection other than the catheter. The incidence of CRBSI varies considerably by type of catheter, frequency of catheter manipulations, and disease-related factors. The incidence of CRBSI remains high despite of the use of aseptic techniques. In a prospective study of 111 HSCT recipients, representing 143 Hickman catheter placements, 44% of patients had positive blood cultures. Most of these (40/63) were coagulase-negative *Staphylococci* suggesting a primary line infection rather than a secondary contamination from a blood-borne source. Other frequently involved microorganisms are *Staphyloccus aureus*, Gram-negative bacteria and *Candida species*.

The clinical diagnosis of CRBSI is difficult as there are no specific clinical signs. The fever itself is a sensitive, but non-specific sign, while exit site reactions are specific but not sensitive. In the absence of other foci a positive blood culture is suspicious, and resolution of fever following removal of the catheter makes the diagnosis even more probable, although not proven.

Full proof diagnosis of CRBSI is possible only after removal and culture of the catheter:

- Roll plate technique used by the microbiology laboratory (semiquantitative, >5 CFU)
- Flush or ultrasound technique used by the microbiology laboratory (quantitative, $>10^2$ CFU)
- Same isolate from blood and catheter tip.

If the catheter is not removed, the diagnosis of CRBSI is established if:

- Same isolate with simultaneous blood cultures from peripheral vein and from catheter blood, with a ratio higher than 3:1 CFU ratio between CVC and peripheral sample
- Same isolate from both lumens with a ratio higher than 3:1 CFU between the two lumens
- Using an automated blood culture system the differential time to positivity of CVC culture versus peripheral blood culture positivity being greater then 2 hours is highly predictive for CRBSI.

There are four main possible mechanisms for developing a CVC related infection:

- Migration of skin organisms at the insertion site into the cutaneous catheter tract with colonisation of the catheter tip
- Contamination of the catheter hub leading to intraluminal colonisation
- Occasionally, catheters may be haematogenously seeded from another focus of infection and rarely
- Infusate contamination.

The most important recommendations concerning the prevention of CVC related blood stream infections are listed in Table 4, based on the guidelines developed in the USA by a working group led by the Infectious Disease Society (12).

5. Haematopoietic growth factors

5.1 G-CSF

Prolonged neutropenia and subsequent infections are the most frequent causes of morbidity and mortality following HSCT. The administration of G-CSF post-transplantation results in a clear clinical benefit by shortening time to engraftment and hence reducing complications associated with neutropenia. However, the optimal way of administration is still debated.

5.1.1 Autologous transplantation

G-CSF has been shown to shorten the time to neutrophil engraftment in several randomised phase III trials. The reduction ranged from 2–9 days. This proved to be independent of the number of $CD34^+$ cells infused. In spite of the common concern that G-CSF administration may delay platelet engraftment, in most of the studies this was not the case. Although most studies did not find significant difference in days of febrile neutropenia, half of the studies demonstrated a reduction of the length of hospitalisation. Several studies aimed to find the optimal time to start G-CSF following autologous PBSCT, assuming that progenitors responsive to G-CSF are not immediately present after PBSCT, so that early post-transplant G-CSF administration might be unnecessary. When comparing the time to neutrophil engraftment between early (from day 0 to day +4) initiation of administration to delayed (from day +5 to day +7) there were no significant differences. Neither were there any differences in days of febrile neutropenia, time to platelet engraftment or in the length of hospital stay. Therefore, delayed starting of G-CSF administration following autologous PBSCT is proved to be equally effective. A few randomised studies compared the safety and efficacy of pegfilgrastim and filgrastim in the auto PBSCT setting. No differences were found in terms of time to neutrophil and platelet engraftment, or in the length of hospitalisation, showing that pegfilgrastim may be an acceptable alternative.

Table 4: **Recommendations for prevention of CVC related blood stream infections**	
Education	Health-care worker education and training for the insertion and maintenance of CVCs is essential. Moreover, periodic assessment of their knowledge of and adherence to guidelines is strongly recommended. Trained personnel for the insertion and maintenance of CVCs should be designated.
Catheters and materials	An important pathogenetic determinant is the material from which the device is made. *In vitro* studies demonstrate that CVCs made of polyethylene or polyvinyl chloride are less resistant to adhesion of micro-organisms than are CVCs made of teflon, silicone or polyurethane. The number of ports must be kept to the minimum required for the patient's management. Cuffed and tunnelled CVCs should be employed if their use is to be prolonged (e.g. allogeneic transplant).
Site of catheter insertion	In adults, a subclavian site is preferred as lower extremity sites are associated with a higher risk of infection (and deep venous thrombosis). Subclavian sites also reduce the risk of infection compared to jugular sites.
Maximal sterile barrier precautions during insertion	Full aseptic techniques should be used at the time of insertion. 2% aqueous chlorhexidine gluconate (preferably), tincture of iodine, or 70% alcohol can be used to prepare the skin before CVC insertion. Organic solvents (e.g. acetone and ether) should not be applied.
Catheter and catheter site care	One port should be designated exclusively for hyperalimentation if a multilumen catheter is used. The routine use of prophylactic intranasal or systemic antibiotics before insertion or during the use of the CVC and antibiotic lock solutions are not recommended. The catheter site can be covered by sterile gauze or a sterile, transparent semi-permeable dressing and the dressings should be replaced whenever they become damp or loosened. Gauze dressings should be replaced at least every two days and transparent dressings every 7 days. The catheter sites must be monitored visually or by palpation regularly and if patients have tenderness at the insertion site and/or fever without obvious source, the dressing should be removed for thorough examination.
Replacement of catheter	Catheters that are no longer essential should be removed promptly. However routine replacement of CVCs to prevent catheter related infections is not advised. CVCs must not be removed on the basis of fever alone. Clinical judgement is required to assess the appropriateness of catheter removal if infection is evidenced elsewhere or if a non-infectious cause of fever is suspected.
Administration set replacement	• Following administration of blood, blood products immediately • Following total parenteral nutrition – after 24 hours • Other fluid sets – after a maximum of 72 hours

5.1.2 Allogeneic transplantation

Several studies have addressed the efficacy of using G-CSF to reduce the post-transplant neutropenic period in allogeneic bone marrow or peripheral blood stem

cell transplantation. In the PBSCT setting all studies demonstrated an improvement of 1–4 days in neutrophil engraftment compared to the control arm. Neither platelet engraftment, nor the number of days with febrile neutropenia differed. The median time period of hospitalisation following transplantation was also similar. Similar results were reported in retrospective observations of patients receiving bone marrow as the source of stem cells. The only different observation concerned the incidence of GvHD. While there was no significant difference in the PBSCT setting, a significant increase in acute GvHD was detected in patients with post transplant G-CSF in two retrospective studies with bone marrow transplantation. However, a meta-analysis including 1198 allo-transplanted patients (with 88% bone marrow graft) did not find an increased incidence of GvHD associated with G-CSF use, so no clear conclusion can be drawn whether the use of G-CSF following allogeneic transplantation has any effect on GvHD incidence (13).

5.2 Erythropoietin

Erythropoietin (EPO) has been used with the aim to accelerate the recovery of red blood cells following stem cell transplantation. This idea was based on the observation that EPO levels after transplantation were lower than calculated for the degree of anaemia. However studies not show any major benefits. In allogeneic transplantation some studies showed a reduction in the median time to transfusion independence, but transfusion requirements were not different. However, in subsets at high risk for transfusion EPO reduced transfusion needs. There may be some benefit in the reduced intensity transplant setting where EPO responsive erythroid precursors may persist following conditioning, but prospective studies are lacking. Because of the modest and mixed results of the studies, most centres do not use EPO in the early post-transplant setting. A few randomised trials have addressed the efficacy of EPO following autologous transplantation. None found a significant reduction of transfusion requirements. The lack of benefit is particularly evident with peripheral blood stem cell transplantation (14).

5.3 Conclusion

Evidence exists in favour of the use of G-CSF in some transplantation settings. Besides stem cell mobilisation, G-CSF accelerates engraftment following autologous bone marrow and peripheral blood stem cell transplantation, thus decreasing hospital stay and overall costs. In allogeneic transplantation the administration of G-CSF is acceptable following PBSCT, but because of a potential risk of GvHD its use is not recommended following allogeneic bone marrow transplantation unless future controlled studies generate more favourable results.

6. Oral mucositis

Oral mucositis (OM) occurs in most patients treated with high-dose therapy and stem cell transplantation. It has been associated with an increased need for total parenteral nutrition and opioid analgesics, prolonged hospitalisation, and increased risk of infection.

Despite the benefits of TPN, mucositis *per se* remains an important clinical problem. It is characterised by mucosal damage ranging from mild inflammation to extensive ulceration, which may affect the oral cavity and other parts of the alimentary tract. Typically, oral mucositis peaks between day 6 and 12, and resolution coincides with engraftment. Mucositis is associated with an increased risk of systemic infection resulting from bacteraemia associated with the breakdown of mucosal barriers. Mucositis-associated pain and infection cause significant morbidity and mortality. Both the severity and the duration of oral mucositis are decreased in reduced-intensity conditioning (RIC) regimens compared to myeloablative HSCT, although considerable differences may exist between different RIC protocols.

6.1. Interventions for the prevention of mucositis

Management of oral mucositis requires a multidisciplinary approach. Basic oral care consists of a pre-transplant oral/dental examination aimed at decreasing the oral infectious and inflammatory burden. It also minimises the need for invasive dental procedures in the immune reconstitution phase. Routine mouth care typically consists of daily assessments by trained nurses using standardised tools to evaluate oral mucositis, pain and other oral complaints. Bland rinses (e.g. water, saline, sodium bicarbonate) are used routinely to remove debris and keep the oral tissues moist. Patients should use a soft toothbrush or dental plaque accumulation should be prevented chemically using chlorhexidine-digluconate solutions (0.05 or 0.12%).

6.2 Intervention for the treatment of mucositis

6.2.1 Pain management

Many patients require narcotics and the length of time of intravenous narcotic need is one of the best indicators of the severity of mucositis. Morphine is recommended as the opioid of choice.

Topical agents are available with or without analgesics including diphenhydramine, corticosteroids, antacids, sodium hyaluronate gel, and mucoadhesive protectants. Unfortunately, the evidence supporting benefit for any of these interventions is absent or weak. One single centre study reported a beneficial effect of a supersaturated calcium phosphate oral rinse solution on the duration and severity of mucositis and pain (15). Amifostine is a phosphorylated aminothiol, which has a protective effect on normal

tissues against radiation and alkylating agent toxicity. It has been reported to reduce mucositis associated with high-dose melphalan in one prospective study and several retrospective studies. There is increasing evidence for the use cryotherapy (e.g. ice cubes) to prevent oral mucositis in conditioning protocols containing high dose melphalan, and some studies indicate a positive effect when used in other conditioning regimens (16, 17).

A biological approach aimed to prevent mucositis is the use of recombinant keratinocyte growth factor (KGF, palifermin, Kepivance®). The efficacy of prophylactic intravenous palifermin was demonstrated in a double blind multicentre trial of 212 patients undergoing autologous HSCT for haematological malignancies. Significantly fewer patients receiving palifermin had grade 3 or 4 mucositis (63 vs 98% with placebo) and the duration of mucositis was shorter (median 6 vs 9 days) (18). These benefits were associated with significantly less use of opioid analgesics and less frequent requirement for TPN support. On the basis of this study palifermin was approved in Europe for the prevention of oral mucositis associated with autologous HSCT.

6.3 Other oral complications

6.3.1 Infection

Oral mucosal infections may be associated with a wide variety of other microorganisms including anaerobic bacteria, fungi and viruses. Dental infections, particularly chronic periodontitis, may also give rise to infectious complications. However, periodontitis can be easily overlooked particularly during neutropenia when local signs of infection are reduced. Chronic GvHD and its treatment increase the risk for oral infections. In oral GvHD, systemic therapies may be combined with local immunosuppressive agents, or local measures alone. Patients with oral cGvHD should be seen regularly by a dental professional as caries is very common (19).

6.3.2 Bleeding

In addition, gingivitis and periodontitis may contribute to bleeding risk during profound thrombocytopenia.

6.3.3 Dry mouth

Reduced saliva production increases risk of dental caries, oral mucosal injury and infections, and affects taste. Palliation includes sugarless gum or sweets, frequent water sipping, non-alcoholic mouthwashes and lip balm or systemic sialogogues (pilocarpine hydrochloride). Because of increased mucosal sensitivity, spices, alcohols, and flavouring agents (especially mint flavours in toothpaste and oral care products) should be avoided. There are also difficulties with chewing and swallowing.

6.4. Conclusion

Oral care should be performed before, during and after HSCT. Several approaches have been tried for the prophylaxis or therapy of mucositis. Although progress has been made, the problem has not yet been solved. A number of new agents promise clinical benefit, either single or in combination therapy.

7. Prevention and treatment of chemotherapy induced nausea and vomiting

7.1 Introduction, classification

The objective of antiemetic treatment is the perfect prevention of nausea and vomiting during the course of the transplant.

For the classification of chemotherapy induced vomiting and the emetic potential of cytotoxic therapy see Table 5 and Table 6.

The high dose chemo/radiotherapy used in standard conditioning regimens (see

Table 5: **Classification of CT induced emesis**

Acute emesis	Delayed emesis	Anticipatory emesis
Occurs during the first 24 h following CT	Occurs later than 24 h	Conditioned response of patients who developed significant nausea and vomiting during previous CT

Table 6: **Emetogenic potential of intravenous antineoplastic agents**

Probability of vomiting*	Agent
High (>90%)	Cisplatin Cyclophosphamide ≥1500 mg/m^2 Carmustine
Moderate (30–90%)	Cytarabine >1 mg/m^2 Ifosfamide Cyclophosphamide <1500 mg/m^2
Low (10–30%)	Mitoxantrone Etoposide Methotrexate
Minimal (<10%)	Busulfan Fludarabine

**in the absence of antiemetic prophylaxis*

Chapter 8) has high emetic potential. In addition, there are several other factors that may further increase the risk of vomiting (consecutive day administration, prior cytotoxic treatment, and other medication, e.g. opiate analgesics).

7.2. Prophylaxis and treatment

The main principles of emesis control are:

- Nausea and vomiting are far easier to prevent than to treat
- Antiemetic therapy should be adjusted for the drug with the highest emetic risk
- The risk for emesis following highly emetogenic chemotherapy lasts approximately 4 days
- Patients must be protected throughout the full period of risk
- Oral and IV formulations have equivalent efficacy.

There are few randomised trials specifically studying the issue of nausea/vomiting in the transplant setting. The neurokinin-1 receptor antagonist aprepitant represents a new class of antiemetic drugs. When used in combination with serotonin antagonists and corticosteroids, aprepitant appears to provide better protection against both acute and delayed emesis in very highly emetic chemotherapy. There is a general consensus that a combination of a serotonin receptor antagonist (ondansetron, granisetron, tropisetron, palonosetron or dolasetron) plus aprepitant and dexamethasone should be the standard prophylaxis during conditioning. Recently, a water soluble form of aprepitant (fosaprepitant) has been approved and can be administered as parenteral alternative to oral aprepitant. In case of failure of the prophylaxis the addition of further dexamethasone (max 20 mg/day) and/or a benzodiazepine (e.g. lorazepam max 4 mg iv) may help to counter increased patient anxiety and possible anticipatory emesis. An alternative is to switch to a different serotonin antagonist, since there is an incomplete cross-resistance between agents (Table 7 and Table 8) (20).

Table 7: **Prevention of conditioning induced nausea/vomiting**

Drug (start before conditioning)	**Administration**
Aprepitant	125 mg PO on day 1 and 80 mg on days 2-3
Dexamethasone	12 mg PO or iv on days 1- until end of conditioning +2 days
5HT3 antagonist (setron)	PO or iv
+ Proton pump inhibitor	All days
+/- Lorazepam or clonazepam (0.5–2 mg)	All days

Table 8: **Treatment of breakthrough emesis**

General principle: give an additional agent from a different drug class
- Metoclopramide 10–40 mg PO or iv every 4–6 h
- Lorazepam or clonazepam 0.5–2 mg every 4–6 h
- Promethazine 12.5–25 mg PO or iv or iv every 4 h
- Haloperidol 1–2 mg PO or iv every 4–6 h
- Change 5H3 antagonist
Exclude other causes:
- GvHD
- *Candida/herpes* esophagitis
- other drugs (imipenem)
- bowel obstruction
- uraemia, etc.

7.3 Conclusion

The conditioning regimens used in HSCT are known to have a high emetogenic risk. A com-bination of a serotonin antagonist (setron) plus a neurokinin-1 antagonist (aprepitant) together with dexamethasone is considered to be the standard prophylaxis.

References

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Multiple Choice Questionnaire

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

1. Which of the following is the most accurate for assessing nutritional status in HSCT recipients?

a) Serum cholesterol ☐
b) Serum glucose ☐
c) Nitrogen balance ☐
d) Anthropometric measurements ☐

2. What is the most common complication of TPN?

a) Elevated liver enzymes ☐
b) Hypertriglyceridaemia ☐
c) Elevated serum creatinine ☐
d) Catheter-related complications ☐

3. What is the most important handling regarding protective environment for all transplant patients?

a) No visitors ☐
b) Use alcohol hand rub ☐
c) Use of gowns and other protective clothing ☐
d) Antiseptic bathing ☐

4. Which of the following is *not* considered a standard indication for the use of G-SF?

a) Stem cell mobilisation ☐
b) To accelerate engraftment following allo-HSCT ☐
c) To accelerate engraftment following auto-HSCT ☐
d) Treatment of secondary neutropenia following transplant due to drug toxicity ☐

5. Which statement is true concerning oral mucositis?

a) Oral mucositis a significant cause of morbidity and mortality after HSCT ☐
b) A pre-transplant oral/dental evaluation prior to HSCT is only necessary in patients with oral complaints ☐
c) Tooth brushing should be discontinued during pancytopenia ☐
d) Oral GvHD is a contraindication to preventative dental care ☐

NOTES