Graft-versus-host disease (GVHD)

A Guide for Nurses

Leukaemia Care
Nurse Academy

Introduction

GVHD is a condition that occurs in patients who have received an ASCT, and where the graft (stem cells from the donor) reacts against the host (patient receiving the stem cells).

An ASCT involves transplanting healthy stem cells from a suitable matching donor such as a sibling, parent or child into a patient with a blood disorder who needs a transplant.

The donor stem cells replace the patients' defective stem cells that have previously been destroyed by treatment with radiation or high doses of chemotherapy, known as the conditioning process.

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ASCTs are performed in patients in conditions such as:

- Acute and chronic leukaemia
- Myelodysplastic syndromes
- Aplastic anaemia
- Non-Hodgkin's and Hodgkin's lymphomas
- Multiple myeloma
- Haemoglobinopathies (blood disorders that affect red blood cells)

Stem cells from the donor are infused into the patient's bloodstream, from where they travel to the bone marrow and start creating new blood cells in a process called engraftment.

Donated blood stem cells can be collected from:

- The donor's blood
- The bone marrow within a donor's hipbone
- A donated umbilical cord

ASCTs are associated with about a 50% rate of transplant-related deaths or life threatening side effects which include GVHD.

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If you would like any information on the sources used for this booklet, please email **communications@leukaemiacare.org.uk** for a list of references.

About Leukaemia Care

Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.

Our services

Helpline

Our helpline is available 9:00am – 5:00pm Monday - Friday and 7:00pm – 10:00pm on Thursdays and Fridays. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500068065** on weekdays 9:00am – 5:00pm.

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemiacare.org.uk** or over the phone on **08088 010 444**.

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.leukaemiacare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/find-a-support-group/**

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some

way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **support@leukaemiacare.org.uk**

Online Forum

Our online forum, **www.healthunlocked.com/leukaemia-care**, is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

Webinars

Our webinars provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support. For information on upcoming webinars, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/onlinewebinars/**

Website

You can access up-to-date information on our website, **www.leukaemiacare.org.uk**.

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@leukaemiacare.org.uk**

Patient magazine

Our magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemiacare.org.uk/communication-preferences/**

What is GVHD?

GVHD is a serious complication that occurs in patients who have had an ASCT.

Both acute and chronic GVHD cause considerable disease and even death.

It affects approximately 30–40% of transplant recipients who have had a matched sibling donor transplant, and up to 65-70% with unrelated donor transplants.

GVHD is caused by the graft reacting against the host. The T-lymphocyte white blood cells (T-cells) from the donor's immune system identify the host's cells as foreign bodies and start an immunological reaction to them and other healthy tissues.

Lymphocytes are white blood cells that are a part of the immune response. There are three types of lymphocytes: B lymphocytes (B-cells), T-cells, and natural killer (NK) cells:

- B-cells produce antibodies that seek out invading organisms.
- T-cells destroy the organisms that have been labelled by the B-cells, as well as internal cells that have become cancerous.
- NK-cells attack cancer cells and viruses

Differences between acute and chronic GVHD

GVHD can be acute (aGVHD) or chronic (cGVHD):

- aGVHD is seen in 50-70% of patients
- cGVHD occurs in 30-50% of patients

Previously, the difference between aGVHD and cGVHD was based on the time of the occurrence of GVHD:

- aGVHD occurred within 100 days after the transplant
- cGVHD occurred 100 days after the transplant, possibly lasting months to years

The difference between aGVHD and cGVHD is now based on clinical manifestations:

- aGVHD commonly occurs in the skin, liver and gastrointestinal tract and may do so in isolation or in combination.
- cGvHD changes occur in the skin, lung, mucous membranes, gastrointestinal tract and musculoskeletal system.

The risk of GVHD occurring can be reduced by:

- Administration of immunosuppressants such ciclosporin, mycophenolate mofetil or tacrolimus for several days before the ASCT and continued for a few months after the ASCT
- After the transplant, another immunosuppressive drug (cyclophosphamide) can be started 3 to 5 days after the transplant.
- Removal of the T-cells from the donor's blood or bone marrow before the ASCT
- Use of corticosteroids to help control the immune system

GVHD which is manageable with treatment is beneficial because it signifies that the new immune system is developing and that the transplant has worked. Therefore, patients who develop GVHD have lower leukaemia relapse rates. This is known as the graft-versus-tumour effect.

Acute GVHD

Despite being differentiated from cGVHD based on clinical manifestations, aGVHD can be classified as the following based on the timing of its occurrence:

Differences between acute and chronic GVHD (cont.)

- **Classic:** within 100 days of the ASCT
- **Persistent:** lasts beyond 100 days
- **Recurrent:** resolves but reappears after 100 days
- **Late-onset:** symptoms start after 100 days

The chance of aGVHD developing is increased by:

The source of the stem cell.

- Older recipient/donor
- A human leukocyte antigen (HLA) mismatched donor
- Even with a fully compatible donor, aGVHD can still occur as there are always minor differences in the HLA proteins between two individuals. The only exception to this is if donor and recipient are identical twins.
- Sex mismatch, specifically a multiparous female donor into a male patient

GVHD rates are lower when using cord blood because the stem cells are not as mature and so do not have to be as well matched.

High-intensity conditioning regimen given to prepare the patient for the ASCT. High-dose chemotherapy, with or without radiotherapy, damages body tissues and creates an inflammation process that leads to the donor T-cells attacking the host's epithelial cells.

Symptoms occur most commonly, either in isolation or in combination, in:

- **Skin:** Rash, dermatitis
- **Liver:** Hepatitis, jaundice
- **Gastrointestinal tract:** Abdominal pain, diarrhoea

A skin biopsy will differentiate GVHD from viral infections (hepatitis or colitis) or skin rash due to drug reactions.

About 50% of patients with aGVHD will progress to cGVHD.

Receipt of donor lymphocyte infusions following an ASCT to treat and prevent relapse can lead to aGVHD in approximately 20-35% of patients and cGVHD in 33 61% of patients.

Chronic GVHD

An increased prevalence of cGVHD is seen due to:

- Increased use of ASCTs in older patients
- Widespread use of blood cells rather than a bone marrow sample
- Improvements in patient survival during the first months after the ASCT

Risk factors for cGVHD include:

- Previous history of aGVHD, however 33% of patients do not have prior aGVHD
- Advanced age of recipient
- Use of matched unrelated donor
- Female donor to male recipient
- Receipt of transfusions prior to transplantation
- Presence of HLA antibodies in recipient's blood
- Composition of the graft, particularly CD3+, CD19+, CD34+ cells.
    - CD (cluster of differentiation) proteins are markers on the surface of cells which enables them to be identified.
    - CD3 is a highly consistent T-cell marker
    - CD19 is a reliable B-cell biomarker, which increases as leukaemia B-cells proliferate
    - CD34 is an important marker for bone marrow stem cells
- Positive cytomegalovirus serology

Symptoms affect mainly the skin and oral mucosa.

Other organs can be affected, but the oral cavity is the main site affected, and in some, the only site affected.

Inflammatory symptoms are like those of acute GVHD, but, as the condition progresses, tissue fibrosis and greater organ involvement occurs.

Diagnosis is by clinical examination with confirmation using a biopsy

What parts of the body does GVHD affect?

Following an ASCT, the commonest organs affected by GVHD are the skin in 75-100% of patient cases and oral mucosa in 80-100%.

Other organs which can be involved are:

- Acute GVHD mainly affects your skin, gastro-intestinal tract and liver.
- Chronic GVHD might affect the skin, liver, eyes, mouth, lungs, gastrointestinal tract, neuromuscular system or genitourinary tract.

GVHD can be graded 1-4 depending on the number and severity of organs affected.

- Grade 1 represents a mild form of GVHD which may not require treatment.
- Grade 4 represents the most severe form requiring treatment with corticosteroids and immunosuppressants.

Skin lesions

aGVHD: Dry and itchy rash like measles on the palms of the hands or the soles of the feet but can affect the whole body. Rash can turn into blisters and vesicles like those of a burn.

cGVHD: Rash and blisters on the face, ears, palms, and soles, or sclerosis (hardening) of the skin, and often in cGVHD, it may remain continuous.

Mucosal membranes

Oral cGVHD:

- Mucosal sensitivity, lichenoid lesions, and hyperkeratotic plaques
- Sclerosis with limited opening of the mouth

Mucosal involvement at other sites:

- Eyes: burning, irritation, dryness, and photophobia
- Vulvovaginal mucosa: redness, dryness, pain, lichen planus changes and strictures
- Penis: irritation, soreness, red plaques on penile head, lichen-sclerosus changes and difficulty retracting the foreskin.

Abdominal swelling and jaundice due to liver injury

Abdominal swelling, jaundice and abnormal liver function test results indicate scarring and damage of the liver.

Liver injury manifests itself as jaundice with itchy skin.

Dry eye syndrome

Dry eye syndrome is a dryness and/or a gritty sensation experienced in the eyes with light sensitivity and excessive watering of the eyes.

Common in both aGVHD and cGVHD, dry eyes are due to inflammation of the conjunctiva and cornea, which leads to reduced tear production.

Intensive treatment for dry eye syndrome may be needed if the syndrome manifests in its most serious form.

Given intense irritation experienced with dry eye syndrome, extreme care is needed to avoid lesions and infections of the cornea.

Dry eye syndrome may be associated with vaginal dryness, which should be treated by a gynaecologist.

Difficulty swallowing, pain on swallowing and weight loss

In both aGVHD and cGVHD, discomfort or pain on swallowing may be experienced. This can impact on the patient's appetite, reducing food intake and causing weight loss.

Problems urinating

An increase in need to urinate and burning/bleeding on passing water is an indication that the patient's genitourinary system is affected.

Lung toxicity

The lung is almost certainly a target organ for aGVHD, although the exact mechanism of aGVHD-induced lung injury is not clear. T-cells and macrophages may play a role and cytokines such as interferons and tumour necrosis factor alpha, which are proteins produced by a variety of cells during an acute inflammation

What parts of the body does GVHD affect? (cont.)

response, are also implicated

Obstruction of small airways in the lungs due to inflammation is a known complication of cGVHD and is called bronchiolitis obliterans syndrome (BOS).

Four criteria must be present for the diagnosis of BOS:

Ratio of FEV1 (forced expiratory volume in 1 second) and VC (vital capacity, volume of exhaled air after maximal inspiration) must be:

- Less than 70% or
- Under the 5th percentile of predicted FEV1 value which is calculated using a spirometry calculator

FEV1 must be less than 75% of predicted FEV1 with >10% decline over less than 2 years.

A respiratory tract infection must be excluded by X-ray, computed tomography (CT) or cultures of sputum/ bronchoalveolar lavage.

One of two other supporting features of BOS:

- Another symptom of cGVHD, such as cutaneous symptoms
- Alternative supporting evidence of BOS such as air trapping seen on expiratory chest high-resolution CT

Symptoms of BOS include tiredness, shortness of breath, wheezing, fever, dry cough and congestion.

Symptoms usually begin around 5 days after the ASCT and start to improve after 2 to 3 weeks.

Other symptoms

Other less common symptoms of aGVHD, which do not respond well to treatment and can become part of, cHVGD are:

- Fasciitis: Inflammation of the connective tissue around the muscles, blood vessels and nerves
- Oral ulcers which do not respond to topical therapies
- Secondary malignancy and early death

What is the treatment for GVHD?

Treatments common to aGVHD and cGVHD

Corticosteroids are the first-line treatment for aGVHD or cGVHD. Patients can be treated with either topical, oral or intravenous corticosteroids depending on their severity.

Extracorporeal photopheresis (ECP) is recommended as a second-line treatment for both aGVHD and cGVHD. ECP is a similar process to apheresis.

Blood removal via a cannula and withdrawal of the white cells for exposure to ultraviolet light (UVA) to destroy those that cause GvHD. The blood is then reinfused into the patient.

An ECP treatment session lasts 1 2 hours with patients attending treatment several times a week. Duration of ECP treatment depends on patients' response.

ECP requires time commitment on behalf of the patients in terms of:

- Regular weekly appointment
- As ECP is not available in all treatment centres, patients are required to travel to other hospitals

Important nursing considerations are:

- Coordination of patients' treatments
- Knowledge of locations where ECP is available and motivation of patients to attend
- Monitoring of patients' haemoglobin levels

Ruxolitinib: When patients do not respond to corticosteroids, ruxolitinib, an oral selective inhibitor of Janus Kinase (JAK)1 and JAK2 is effective for treating both aGVHD and cGVHD. It is also an option for patients who cannot access ECP treatment.

Immunosupressants:

- Tacrolimus, sirolimus and ciclosporin are used for prophylaxis and treatment in aGVHD and cGVHD.
- Mycophenalate is generally used as prophylaxis and treatment in cGVHD

Prevention in the first instance is the main approach to GVHD management.

What is the treatment for GVHD? (cont.)

Treatment for aGVHD

Treatment with corticosteroids is the first line treatment for aGVHD, with ECP being second-line treatment.

Steroid treatment failure is considered to have occurred when there is symptom improvement after 3–7 days of treatment. Despite no international consensus, immunosuppressants are generally added at this point.

The three main organs affected by aGVHD are the skin, liver and gastrointestinal tract.

Cutaneous aGVHD

Strong topical corticosteroids may be effective for mild cutaneous aGVHD symptoms, but high-dose systemic corticosteroids are generally required for more severe symptoms.

It is also important to be aware of possible wound infections in cutaneous aGVHD. Treatment with the appropriate antibiotics according to the skin culture is essential

Liver aGVHD

Jaundice resulting from liver injury does not require any specific treatment, apart from blood transfusions to recover normal levels of red blood cells and platelets.

If not already done, review of any hepatoxic medications is important.

Gastrointestinal aGVHD

Sickness, abdominal pain and diarrhoea can be treated with anti-emetics and painkillers.

Fluid and nutrition management is vital. Dehydration and weight loss prevention may require IV fluids and feeding through a nasogastric tube if the patient cannot eat and is losing weight.

Total parenteral nutrition and referral to a dietitian is important.

Treatment for cGVHD

Systemic corticosteroids are used as first-line treatment in cGVHD, but they are only effective in 50% of patients. In addition, they are limited due to their side effects during the long-term treatment

required in cGVHD.

Second-line treatments for cGVHD include ECP and sirolimus, particularly for patients who are:

- Steroid-refractory
- Developing serious side effects to corticosteroids
- Considered steroid-dependent

Corticosteroid treatment for cGVHD may be supplemented by topical or skin directed treatments that include topical calcineurin inhibitors such as tacrolimus, psoralen activated by ultraviolet A (UVA), or irradiation with UVA1 or UVB.

Symptoms of cGVHD generally affect:

- Skin, mucous membranes, eyes
- Gastrointestinal tract
- Lung (scarring of lung tissue with reduced lung function)
- Musculoskeletal system

cGVHD may present with a wider range of symptoms including raised liver enzymes, pericarditis, and loss of blood cells (red, white, and platelets).

In addition to systemic corticosteroids and ECP, systemic immunosuppressants are often needed to treat cGVHD. However, as with systemic corticosteroids, they can involve troublesome side effects as they need to be given long-term

Nursing challenges with GVHD

Nursing care of patients who have undergone an ASCT is complex and challenging, particularly when they have GVHD complications. Effective nursing care can improve patient survival and offer them a better quality of life during treatment.

Nursing challenges for ASCT patients with GVHD include:

- Assessing patients' needs
- Recognition of GVHD symptoms and knowledge of the treatment, management, and psychosocial care needed for patients with these symptoms
- Knowledge of expected and less common side effects
- Consistent coordination of patient care for prolonged periods, if required
- Tailoring of nursing care to the degree of skin damage with decisions made about hygiene, topical or systemic treatment, infection prevention, relief of discomfort, functional ability and body image alteration.
- Education of patients on the importance of sun protection and recognition of the risks for skin and oral cancer.
- Provision of support for patients whose disease is refractory to cGVHD treatment
- Support is required for patients who need to remain on low dose oral steroids for life to control their cGVHD. Consequences of long-term steroid use, particular in children have been clearly documented, and harmful side effects in the long term on growth and bone density need to be managed.

Specific nursing considerations

Skin

In addition to systemic treatments for cutaneous GVHD, nurses can offer topical management techniques as well as general care to relieve cutaneous symptoms of aGvHD.

- Prevention of skin breakdown by applying lotions and/or moisture barriers
- Sensible use topical steroid creams
- Care of open, blistered or extensively involved patches of skin
- Education of cGVHD patients on risks from sun exposure and advice on use of high sun protection factor sunscreens.
- Validation of distress and reassurance of the symptoms due to mucosal involvement of genital skin which can affect patients' body image and impact on their relationships.
- cGVHD can cause skin thickening around the joints with limited movement. Advice on appropriate exercises and referral to a physiotherapist is needed.

Liver

- Limiting use of hepatotoxic medications
- Providing information on liver biopsy, if required
- Control of itching with antihistamines and topical steroidal or non-steroidal creams

Gut

- Meticulous recording of fluid intake and output, daily weight and serum electrolytes test results
- Detection of gastrointestinal bleeding by testing vomit/stool for occult blood
- Monitoring of the patient's levels of haemoglobin, haematocrit and platelet counts
- Management of faecal incontinence to prevent skin breakdown with thorough cleansing of the skin following defaecation and application of moisture barrier cream
- Psychological support for patients trying to manage self-

Specific nursing considerations (cont.)

esteem problems related to incontinence, skin appearance and coping with serious ASCT complications

Lung

Treatment of lung cGVHD includes inhaled corticosteroids, systemic steroids, bronchodilators and referral to a physical rehabilitation programme.

The outlook for lung cGVHD is generally poor as it does not respond to many of the existing treatments.

Patients' distress and anxiety at increasing breathlessness can be helped by nurses and physiotherapists instructing breathing techniques, stress management and focused relaxation to help patients self-manage.

Psychological support

Clinical and psychological nursing support of patients and their families, during and after their experience of GVHD is essential and requires complex management and expert nursing skills.

Nurses can provide comprehensive understanding and help for patients and their families who following the relief of the promise of a cure with an ASCT, are faced cGVHD.

Follow-up

Follow-up of patients who have experienced aGVHD or cGVHD is an important element of the management.

Careful monitoring of GVHD patients for signs of complications is a crucial role for haematology nurses as they spend more time with patients.

The care of patients is often shared between oncologists, haematologists, clinical nurse specialists, physiotherapists, dietitians and other haematology healthcare team members, such as dermatologists, gastroenterologists and respiratory specialists, where applicable. This allows for decisions on the appropriate follow-up care which is coordinated by the haematology clinical nurse specialist.

Abbreviations

aGVHD

Acute graft-versus-host disease

ASCT

Allogeneic stem cell transplantation

BOS

Bronchiolitis obliterans syndrome

CD

Cluster of differentiation

cGVHD

Chronic graft-versus-host disease

ECP

Extracorporeal photopheresis

FEV1

Forced expiratory volume in 1 second

GVHD

Graft-versus-host disease

NK

Natural killer

UVA, UVA1, UVB

Ultraviolet A, Ultraviolet A1, Ultraviolet B

Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

Around 34,000 new cases of blood cancer are diagnosed in the UK each year. We are here to support you, whether you're a patient, carer or family member.

Want to talk?

Helpline: **08088 010 444**
(free from landlines and all major mobile networks)

Office Line: **01905 755977**

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