

CURE SICKLE CELL.

CONDITIONING:

Preparing for Gene Therapy

Sickle cell disease (SCD) is a genetic disorder that affects the shape of red blood cells by changing them from a normal, round shape to a sickle shape. The cells used in gene therapies, called “stem cells,” come from a patient’s bone marrow—the soft spongy area in the larger bones of the body—and are responsible for developing all cell types that make up the blood (red blood cells, white blood cells, and platelets). The stem cells are genetically modified in the lab and then returned to the patient so that they eventually produce healthy, round red blood cells in addition to all the critical cells found in the blood.

To be able to receive these new therapies, patients must first undergo a process called conditioning to make space for the newly modified stem cells within a patient’s bone marrow. This procedure is also commonly used in bone marrow transplants for SCD. The current standard approach used for conditioning involves giving the patient chemotherapy to remove diseased stem cells and create space in the bone marrow.

Common Types of Conditioning Regimens¹

The optimal conditioning strategy for SCD has not been fully established.² Gene therapy trials condition a patient’s bone marrow by using either a “myeloablative” or a “reduced intensity” approach. The goal of a reduced intensity regimen is to lessen side effects; however, this needs to be balanced with making enough space, so the genetically modified cells fit back into the bone marrow. A patient cannot choose the type of conditioning regimen received when enrolling in a clinical trial.

MYELOABLATIVE CONDITIONING

Myeloablative—meaning the bone marrow (myelo-) is significantly reduced (-ablative). This approach commonly uses the chemotherapy medication, Busulfan. After receiving Busulfan, a patient’s bone marrow typically does not recover without receiving stem cells through an infusion.³ All myeloablative conditioning regimens have side effects that can be life-threatening.²

REDUCED INTENSITY CONDITIONING

This approach commonly uses the chemotherapy medication, Melphalan, and is considered a milder conditioning regimen where the bone marrow is partially reduced. This type of conditioning reduces a patient’s bone marrow to a lesser extent,⁴ but it still affects the bone marrow’s ability to regenerate on its own.² Using a reduced intensity conditioning regimen may lessen organ toxicity,¹ but still has severe and lasting side effects.

Short and Long Term Risks of Conditioning

MYELOABLATIVE CONDITIONING

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All myeloablative conditioning regimens have side effects that can be life-threatening.² Below is a list of the most common treatment complications associated with Busulfan.

POTENTIAL IMMEDIATE OR EARLY-ONSET EFFECTS:⁵

Skin / dermatological:

- Hair loss (alopecia)
- Rash
- Skin darkening (hyperpigmentation)

Gastrointestinal:

- Diarrhea
- Dry mouth
- Mucositis (mouth sores)
- Nausea, vomiting

Serious infection

Bleeding (anemia)

Liver damage (hepatotoxicity)

Hypersensitivity

Lung damage (shortness of breath, cough)⁶

Dizziness or blurred vision⁷

POTENTIAL LATE-ONSET EFFECTS:⁷

Dental and oral abnormalities

Fertility complications:

- Testicular hormonal dysfunction
- Impaired sperm production (spermatogenesis)
- Ovarian hormone deficiencies
- Reduced ovarian follicular pool

Cancers:

- Acute myeloid leukemia or solid tumors
- Myelodysplasia

Lung damage (pulmonary fibrosis)

Cataracts

Seizures²

Liver damage (hepatotoxicity)

Bone damage

- Osteonecrosis, avascular necrosis
- Reduced bone mineral density (BMD)

Kidney damage

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a reduced intensity conditioning regimen may lessen organ toxicity,¹ but still has severe and lasting side effects. Below is a list of the most common late treatment complications associated with Melphalan.

POTENTIAL IMMEDIATE OR EARLY-ONSET EFFECTS:⁸

Skin/dermatological:

- Flushing
- Hair loss (alopecia)
- Rash
- Skin darkening (hyperpigmentation)
- Injection site reaction and necrosis

Gastrointestinal:

- Diarrhea
- Mucositis
- Nausea, vomiting

Liver damage:

- Hepatitis
- Jaundice

Musculoskeletal complications

Kidney damage (creatinine increase)

Lung damage (pneumonitis)

Wound healing complications

Cardiovascular:

- Bleeding (hemolysis)
- Inflammation of blood vessels (vasculitis)

Hypersensitivity leading to severe allergic reaction (anaphylaxis)

POTENTIAL LATE-ONSET EFFECTS:⁷

Dental and oral abnormalities

Fertility complications:

- Testicular hormonal dysfunction
- Impaired sperm production (spermatogenesis)
- Ovarian hormone deficiencies
- Reduced ovarian follicular pool

Cancers:

- Acute myeloid leukemia or Solid tumors

Lung damage (pulmonary fibrosis)

Liver damage (hepatotoxicity)

Bone damage:

- Osteonecrosis, avascular necrosis
- Reduced bone mineral density (BMD)

Kidney damage

Steps in the Conditioning Process

Before

LIFE PLANNING

A patient undergoing gene therapy will be in the hospital for several weeks, and it is recommended that life planning should also be a part of preparation. This includes making plans regarding family, home, finances, pets, and employment. It is also suggested that patients complete a legal document called an “advanced directive” (including living will, durable power of attorney, and healthcare proxy) to describe the type of care to be received in case the patient is unable to communicate. A lawyer or social worker should be able to provide guidance on these documents.⁴

MEDICAL PROCEDURES

A physician will conduct exams and tests to make a comprehensive health evaluation of the patient to be sure that they are able to have the procedure. Mental health should also be a part of this screening.^{9,10}

In addition to the chemotherapy medication, several other drugs are required before, during and after the procedure that help reduce side effects of conditioning. To avoid multiple intravenous (IV) lines and needle sticks, a thin flexible tube, called a central line, will be placed into a large vein in a patient’s upper chest. Once the central line is placed in the patient, it is important to keep the area clean and watch for signs and symptoms of infection. Patients should ask their physician how to properly care for their central line.^{6,4}

After

Patients stay in the hospital for several weeks so physicians and nurses can monitor their recovery. After conditioning takes place, a patient is at a high risk of developing a life-threatening infection and other complications. Patients typically stay in a special hospital room and receive preventative treatments to limit the chances of developing these side effects. Once the patient is ready, the genetically modified stem cells are given back to the patient through an infusion. The patient continues to be monitored throughout this process. In addition to the follow up required for the gene therapy clinical trial, routine long-term care is critical for patients that undergo conditioning due to the potential late effects that can result from going through this process. It is critical for patients to monitor their health continuously for years to come and discuss any potential complications that may arise with their physician.

Other Important Effects

FERTILITY

A patient's fertility, or ability to have children, is affected by the chemotherapy used in conditioning. As noted in the "Potential Late-Onset Effects" section, both Busulfan and Melphalan are toxic to the sexual reproductive organs of patients, which result in significantly reduced fertility or complete infertility.^{1,3}

Some trials offer fertility preservation (sperm banking, ovarian tissue preservation, or embryo preservation) for patients enrolled in the trial. Patients should discuss these options with their physician before undergoing conditioning.

INFECTION RISK

It is critical that pre-treatment evaluation include infectious disease screening. Myeloablative conditioning has a high risk of serious infection;¹ however, reduced intensity conditioning still poses an infection risk. Life-threatening infections can occur due to the patient's temporary loss of their ability to produce white blood cells, the cells that fight off infections, as a result of the chemotherapy. While patients undergo conditioning, it is very important to reduce exposure to bacteria, viruses, and fungi. Patients are typically placed in protective isolation in a private room using special air filtration. Special precautions are required to reduce the chance of infection including limiting visitors, prohibiting gifts (plants, flowers, etc.), increased handwashing procedures, diet restrictions, and taking preventative medications such as antibiotics, antivirals, and antifungals.⁶

NOTES

- 1 Majhail et al. Bone Marrow Transplant. 2012 March ; 47(3): 337-341. doi:10.1038/bmt.2012.5.
- 2 UpToDate.com. HCT in SCD
- 3 UpToDate.com. Preparative regimens for HCT
- 4 Leukemia and Lymphoma Society: Blood and Marrow Stem Cell Transplantation
- 5 CCO Health Canada Foundry Formulary: Busulfan
- 6 AHPON medication factsheet 5th edition

- 7 Childrens Oncology Group LTF Guidelines for survivors of childhood, adolescent, and young adult cancers
- 8 CCO Health Canada Foundry Formulary: Melphalan
- 9 UpToDate.com Patient Education: Hematopoietic cell transplantation (bone marrow transplantation) (beyond the basics)
- 10 Pre-gene Therapy Assessment of Patient Readiness and Resilience: Best Practices and Recommendations for Implementation in Sickle Cell Disease