MYELOMA CANADA
MAKING MYELOMA MATTER

InfoSheet

MANAGING CYTOKINE RELEASE SYNDROME (CRS) ASSOCIATED TO TREATMENT

Unlike chemotherapy, myeloma immunotherapy better targets myeloma cells and spares most healthy cells. It helps your immune system recognize and destroy myeloma cells.

Because of the way myeloma immunotherapy works in the body, some of the side effects that may occur are different from those seen in conventional myeloma treatments. These may include, among others: infusion or injection-related reactions, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), other neurologic events, infections, gastrointestinal problems, damage to nerves (peripheral neuropathy), lower blood cell counts, abnormal levels of minerals, and other potential more specific side effects such as temporary vision or skin problems.

This InfoSheet will give you more information about the cytokine release syndrome and the way it affects your body. We will learn how to recognize its signs and symptoms, better manage its undesirable effects on the body and limit the damages.

Definition and causes of CRS

Cytokine release syndrome, or namely CRS, is a severe and sudden inflammatory syndrome caused by a large, rapid and excessive release of cytokines into the blood. Cytokines are small proteins that play a crucial role to combat infections. However, the presence of too many cytokines can cause inflammation and an overreaction of the immune system.

This reaction often happens after an infection (e.g. COVID-19) but it is also observed with certain treatments associated with cancers. More precisely, such complication can occur after certain T-cell-engaging (TCE) immunotherapies such as Chimeric Antigen Receptor (CAR) T-cell therapies, like idecabtagene vicleucel and ciltacabtagene autoleucel, and bispecific antibody therapies, notably elranatamab, talquetamab and teclistamab, being investigated for myeloma. In this regard, the infusion of CAR-T cells or the injection of bispecific T-cell engagers trigger the activation of T-cells (also called T lymphocytes) binding them to the tumour cells.

CRS usually occurs within the first few doses of bispecifics or CAR-T (most frequently within the first 14 days) and typically happens before or at the same time as the neurotoxicity syndrome. The degree of CRS is graded on a scale of 1 to 4, based on the key symptoms and signs of fever and blood pressure. Grades 1 and 2 are considered mild, while Grades 3 and 4 are severe to life-threatening and require admission to the hospital in an intensive care unit to ensure patients are given medications to boost their blood pressure. Fortunately, most cases of CRS are Grades 1-2, and generally respond very well to treatments designed to reduce inflammation while calming immune system activation.

Signs and symptoms of CRS

You should inform your healthcare team if you experience any of the signs and symptoms below (particularly if you are currently on CAR-T cell or on a bispecific antigen treatment):

- Fever, chills and aches (similar to flu symptoms)
- Difficulty breathing
- Dizziness
- Nausea
- Tachycardia (fast heartbeat)
- Low blood pressure
- Low blood oxygen concentration (desaturation)
- Fatigue
- Multi-organ failure

Most often CRS is characterized by fever, a drop in blood pressure and/or a reduction in blood oxygen concentration (desaturation). These signs and symptoms will enable the healthcare team to establish a diagnosis of CRS (Figure 1).

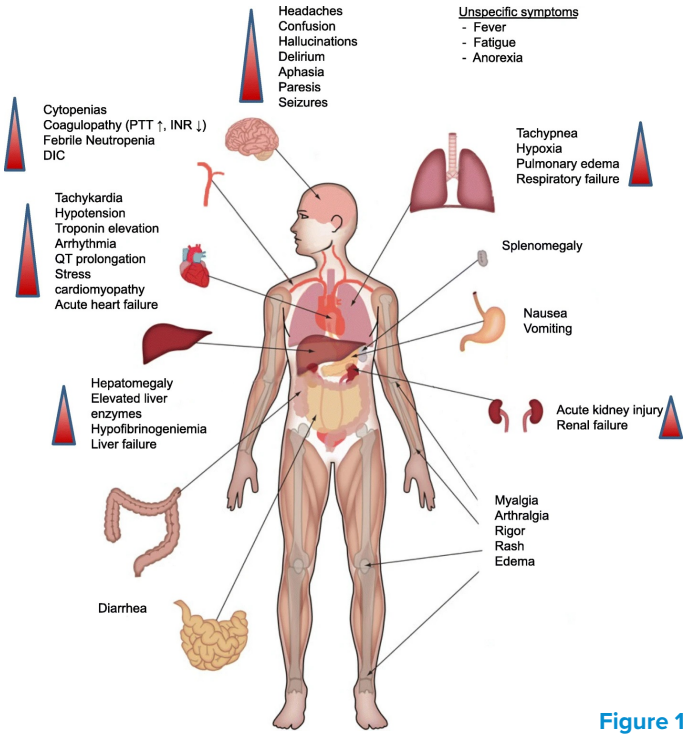

Figure 1

How is CRS treated?

Though most CRS cases are manageable, prompt diagnosis and management of symptoms are essential to prevent serious complications and improve patient outcomes.

Management is based on the type of symptoms (grade of CRS) and how severe they are.

At first, supportive care (e.g. acetaminophen, etc.) is provided to bring down the temperature and manage the inflammation. Intravenous fluids can also be given if needed (Grade 1-2).

If symptoms become more severe or life-threatening (Grade 3-4), for instance if you have trouble breathing, oxygen replacement treatment and a drug named tocilizumab to actually treat the CRS may be necessary to act against the inflammatory mediators and make the response less severe. Tocilizumab is an interleukin-6 (IL-6) receptor inhibitor that can be given alone or combined with steroids (e.g. dexamethasone) when CRS progresses.

Beyond this point, if you need more oxygen support or if the blood pressure drops too low and you need to get medication to bring it back up, monitoring will be necessary.

Tips for self-management and prevention

The best preventative measure is to optimize your health as much as possible ahead of time. Be in optimal physical shape prior to going into CAR-T cell therapy or bispecifics.

Prophylactic measures, such as using tocilizumab and/or administering steroids (e.g. dexamethasone) prior to each dose of bispecific antibodies and CAR T-cell therapy to prevent CRS are being tested in research projects. Preliminary results from these research projects seem to demonstrate a reduction in the incidence of CRS with these preventive treatments[1].

[1] Rosinil L et al. IMS 2024 Brazil; Trudel S, el al. ASH 2022

Also, in attempt to minimize the side effects and reduce the likelihood of CRS or ICANS, bispecific antigen therapy uses a step-up dosing strategy. This means that the patient will receive an initial reduced dose of the drug to allow the person's immune system to slowly become familiar with the new medication. The step-up schedule given over several days helps prevent an overreaction of the immune system and therefore reduces the risk of CRS. These first progressive doses can be given on an outpatient basis, or the patient can be hospitalized.

These treatments, like other anti-myeloma drugs, may also increase your risk of infections on a long-term basis. Here are some other considerations to take in order to prevent infections:

- Complete any outstanding vaccinations at least 2 weeks before starting therapy to prevent influenza, pneumococcal infection, zoster or COVID-19.
- Consider intravenous gamma globulin (IVIg) supplementation for infection control.
- Consider an anti-virus treatment (e.g. valacyclovir) to prevent shingles.
- Myeloma patients have an increased risk of developing *Pneumocystis jirovecii* pneumonia (PJP) than the general population. Prophylaxis with a drug such as trimethoprim-sulfamethoxazole (Septra) or other alternatives is recommended.
- As Cytomegalovirus (CMV) can occur in people with weakened immune systems, it is preferable to check its viral load on a regular basis using blood tests.

Precautionary measures

- Inform your healthcare team of any new or concerning aforementioned symptoms, especially if you have fever or if your blood pressure drops.
- Some of these side effects can be potentially serious. Patients need to be monitored frequently for early indications of side effects and given rapid intensive care and supportive treatment if needed.
- Infection prophylaxis with granulocyte colony-stimulating factors (G-CSFs), used for treating chemotherapy-induced neutropenia, should be used with caution during step-up phase and in case of CRS.
- Your healthcare team may hold treatment in case of active infection or if significant CRS and/or ICANS occur.
- Do not stop or adjust medications without discussing it with your healthcare provider. They may change your dose or schedule of medication to help reduce your discomfort.

To learn more about CAR-T cell and bispecific antigen therapies, consult Myeloma Canada's "**Myeloma Immunotherapy**" and "**Clinical Trials: are they an option for me?**" InfoGuides in the Resource library at www.myeloma.ca.

Your healthcare team and your pharmacist, are also there to support you. It's important to share your symptoms with them.

Reference:
Figure 1: Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. *Cytokine release syndrome. Journal for ImmunoTherapy of Cancer.* 2018;6:56. doi: 10.1186/s40425-018-0343-9

Myeloma Canada wishes to acknowledge and thank Dr. Jean-Sebastien Claveau, Hematologist at the Maisonneuve-Rosemont Hospital (QC), for his contribution. The information disclosed in this InfoSheet is based on existing Myeloma Canada publications reviewed by healthcare professionals and other publications from our sister myeloma organizations: the International Myeloma Foundation (IMF) and Myeloma UK. This information is not meant to replace the advice of a medical professional; they are the best people to ask if you have questions about your specific medical/social situation.