TITLE:

Valganciclovir Four Weeks Prior to cART Initiation Compared to Standard Therapy for Disseminated Kaposi Sarcoma

NCT NUMBER: NCT03296553

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INFORMED CONSENT

We invite you to participate in a clinical research study. Your participation in this study is completely voluntary. No one can force you to participate. If you decide not to participate, nor will it change the medical care to which you are entitled at the National Cancer Institute. Before deciding whether or not to participate, please read this consent letter carefully and ask any questions you may need to resolve any concerns you may have. At the end of this letter of consent is a list of the rights of people involved in research.

Once you understand what this study means, you can decide whether or not to participate. If you agree to participate, you will have to sign and date this informed consent letter.

Kaposi's sarcoma is considered a type of cancer associated with AIDS, and it is caused by another virus called human herpes-virus 8 or Kaposi's sarcoma virus (HVH-8). Infection with the Human Immunodeficiency Virus (HIV) favors the development of Kaposi's sarcoma.

Currently the treatment for Kaposi's sarcoma is multiple antiretroviral drugs against HIV, called highly active antiviral treatments (HAART). These HAART schemes prevent the virus from multiplying in the body and this allows patients to improve their defenses destroyed by HIV (CD4 lymphocytes increase their number).

However, in patients who arrive with very low CD4 levels (less than 100), the initiation of HAART may cause a worsening in some patients who have another active infection such as tuberculosis, tuberculous meningitis or infection of the retina by Cytomegalovirus (this is a virus of the herpes virus family that affects patients with a very altered defense system).

It is complex to understand, but the deterioration is caused because the individual's defenses improve in response to HAART and as there are more defense cells they cause greater inflammation and this damages the affected organs. For this reason, management protocols have been designed where the infection is initially treated and the onset of HAART is delayed for at least two weeks or until the inflammation in the retina, meninges or in any other organ has

decreased. This makes it possible to avoid these serious consequences in most patients. In patients with Kaposi's sarcoma that affects the lung, and / or lymph nodes or who have more than 30 skin lesions. This phenomenon has also been described with worsening of the lesions when HAART is started.

This study aims to see if it is possible to prevent the worsening of the lesions of disseminated Kaposi Sarcoma, if the patient is first treated with an antiviral drug that has activity against the human herpes virus 8 (HHV-8), the causative agent of sarcoma of Kaposi.

Objectives of the study

We want to compare two types of treatment: one group of patients will be treated according to current standards with HAART and if necessary chemotherapy based on bleomycin and vincristine, and a second group will first receive ganciclovir or valganciclovir, the treatment for HVH- 8, and HAART will start when the HHV-8 viral load in the blood has significantly decreased. This group will also receive chemotherapy with bleomycin and vincristine if required.

The assignment to which group you will enter is done by lottery, which is appropriate since it is not known at this time which of the 2 treatments is preferable. You yourself will take out the paper that will be assigned to you and no one from the research group will have access or will be able to change the group that will be assigned to you in the draw.

Study procedures

If you are eligible and agree to participate, you will sign and date this consent letter.

Patients with a diagnosis of HIV and severe Kaposi Sarcoma will be included according to the following criteria: generalized lymphedema (swelling of all or several parts of the body, for example legs and face), and / or more than 30 Kaposi Sarcoma lesions in the skin, and / or that there are Kaposi Sarcoma lesions in the digestive tract visualized by means of an endoscopy study, or suspicion of Kaposi Sarcoma lung involvement by computed tomography study or / and some nuclear medicine study such as PET when it is suspected that his lymph nodes are affected by this disease or scintigraphy with Gallium when it is suspected that the lung is affected.

Your doctor will take a complete medical history and physical examination and you will be asked for a series of studies, most will have to be done even if you are not participating in the study in order to evaluate you properly. An initial evaluation will be performed to define the extent of Kaposi's sarcoma, including:

- Number and documentation by photography of the skin lesions, with biopsy and histopathological report of Kaposi's Sarcoma.
- Blood sample for laboratory tests, including CD4 cells and HIV viral load.
- Performing endoscopy of the stomach and esophagus with taking a biopsy of suspicious lesions of Kaposi Sarcoma.
- Performing endoscopy of the large intestine with taking a biopsy of suspicious lesions of Kaposi's Sarcoma.
- Tomography (CT) of the chest only when it is suspected that the lung is affected by Kaposi's Sarcoma or some other related disease such as tuberculosis or others.
- PET in case the lymph nodes are suspected of being affected by Kaposi's sarcoma.

The presence of other infectious diseases such as syphilis, tuberculosis, toxoplasmosis, cytomegalovirus, and hepatitis will be searched extensively. These are procedures that are performed on patients even if they do not enter the study. For this, the following will be measured: basal serum VDRL and antitreponemal antibodies (blood) (to investigate syphilis). In those patients with positive VDRL, a lumbar puncture should be performed to extract cerebrospinal fluid and perform VDRL on it. Profile of viral hepatitis B and C (blood). Basal toxoplasma serologies (blood). Cryptococcal serum antigen in patients with less than 100 CD4 (blood).

Only in those cases with lung lesions, bronchoscopy, bronchi alveolar lavage will be performed (this study consists of introducing a thin flexible tube that allows visualizing the interior part of the lung and injecting water, which is later recovered to order study) and taking a lung biopsy at the discretion of the researcher.

The identification of any opportunistic disease will receive the appropriate treatment stipulated by the management guidelines.

They will be measured at baseline (the day the study begins) and at weeks 1, 2, 4, 8, 12, 16, 24, and 48 markers of inflammation related to the response of cytosines (they are substances that are produced in the body when there is inflammation and are described below) known in Kaposi's Sarcoma, to assess the inflammatory status of the patient, such as: Viral load for HHV-8, C-reactive protein, D-dimer, IL-6, Il- 10, TNF (blood).

Assessment by the ophthalmologist (eye specialist) at the baseline visit, at 2 and 4 weeks and thereafter at the discretion of the ophthalmologist.

To obtain the samples, a vein will be punctured in your arm, as is usual. All these tests would be done to you if the treating doctor so considered it even if you decide not to participate in the study, except for taking blood for viral load of HHV-8, IL-6, IL-10 and TNF.

The results of all these tests may take a few days, but you will be informed of all of them as the results are available. A total of 38 patients distributed in each group of 19 people will be included.

Risks and discomforts

The disease that you suffer from is serious and your life is at risk regardless of the medical interventions to try to help you, it is hoped to reduce this risk but only in the course of the investigation will we know if this risk was reduced with the proposed treatment. The tests to which you will be submitted involve some discomfort, all these procedures would be done for the management of your disease regardless of your participation in the study.

Your doctor will do everything possible to lessen the discomfort and will be attentive to any problems. It is important for you to understand that whether you participate in the study or not, these tests are important to your health and your doctor would recommend them anyway.

Benefits of participation

The procedures to be done in this study are the same as if you were not in the study. However, with your participation, you can help increase medical knowledge, which could help other patients with the same disease in the future.

Compensation and costs

You will not be paid anything for your participation in the study. In the event of a health problem arising from your participation in the study, you will receive medical care at no cost to you at INCan. Also, all tests will be done at no cost to you.

The tests related to this study will be done at no cost to you and will be provided to you. free administration of ganciclovir or vagnacilcovir in the corresponding case and the payment of the medications that are required for the management of adverse events related to the use of two medications such as the colony stimulating factor in case of low white blood cells . You will receive antiretrovirals through the universal access program that corresponds to your place of residence and will be processed by the INCan Infectious Diseases group. Participation in the study does not imply the administration of other drugs not related to Kaposi Sarcoma and its treatment or the free provision of other services by INCan.

Responsibilities of the subject

You will need to go to study visits, follow the instructions your doctors give you, and take the study drug as directed.

You should not participate in any other study while you are in this one.

Confidentiality

Your participation in this study will be recorded in your medical record, but will not be disclosed. Researchers, members of the ethics committee that approved the study, and representatives of health authorities may have access to your medical record for verification purposes. If the results of the study are published, it will be in a scientific journal and you will not be identified by name.

Contact persons

If you have questions about this study, or if you think you have been injured as a result of it, please contact Dr. Patricia Volkow 554747-1020 ext. 12110.

If you have questions about your rights as a participant in research, please contact Dr. Myrna Gloria Candelaria Hernández of the Research Ethics Committee of the National Cancer Institute or Dr. Alejandra Monroy López 56280400 extension 37015, regarding For any technical aspect of the study that will be carried out, contact Dr. Patricia Volkow 47471020 extension 12110 or the cell phone 5560989351.

CONSENT

I have read and understand the above information about this study. I have been able to ask questions, which have been answered to my satisfaction. I understand that my participation is voluntary, and that I may refuse to participate or leave the study at any time, without prejudice to myself or my health care rights. I freely agree to participate in the study. I will receive a signed copy of this informed consent letter.

Participant Name	*Signature*	*Date*
Name who obtained consent signature	*Signature*	*Date*
Witnes #1 Name	*Signature*	*Date*
Witnes 2 Name	*Signature*	*Date*