TITLE:

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

NCT NUMBER: NCT03296553

DATE : JULY 23, 2015.

STUDY PROTOCOL

Objective:
To evaluate the occurrence of severe immune reconstitution inflammatory syndrome associated to Kaposi Sarcoma (S-IRIS –KS) and it´s attributable mortality in patients with AIDS and disseminated KS (dKS) (pulmonary and/or skin disseminated, and/or lymphadenopathic, and/or generalized lymphedema, and/or gastrointestinal tract involvement) with the use of valganciclovir (ganciclovir prodrug, oral formulation) prior to the initiation of combined antiretroviral therapy (cART) compared with the standard management of immediate cART initiation.

Hypothesis:
In patients with AIDS and disseminated KS administration of valganciclovir as an anti-HHV-8 agent can diminish viral replication prior to administration of cART, and thus decrease the frequency of S-IRIS-KS with a subsequent reduction on S-IRIS-KS attributable mortality.

Methodology:
Open randomized clinical assay. Will include patients with AIDS and disseminated KS who accept to participate and sign informed consent.

Inclusion criteria:
Patients >18 years old, HIV+ naïve to cART with dKS, able and willing to provide written informed consent.
DKS was defined as the presence of KS pulmonary disease and/or ≥30 KS skin lesions, with or without lymphedema, and/or lymph node involvement, and/or gastrointestinal tract KS involvement (biopsy-proven at least in one site).

Exclusion criteria:
Another concomitant malignancy, Multicentric Castleman Disease (MCD), steroid treatment two months prior to screening, active Hepatitis B, Hepatitis C or CMV end-organ disease infection, and/or severely ill patients with APACHE II score >15 points.

The study will comprise two study groups:
1. Group 1: Patients will receive treatment with valganciclovir during 4 weeks prior to initiation of cART and/or continue for 48 weeks
2. Group 2: Patients will initiate standard treatment with cART.

Both groups receive chemotherapy with bleomycin/vincristine; according to treating physician.

Randomization
Patients will be randomized by blocks of ten; the assigned group written in closed envelopes:
Experimental Group 1 (EG) will receive valganciclovir 900 mg twice daily for 48 weeks and initiate cART at week 4 after randomization.

Control Group 2 (CG) will start cART immediately according to current Mexican Guidelines.

Blinding:
No blinding was considered feasible for personnel or patients; this is an open label study.

Sample Size
Sample size was calculated for a study power of 80% and an alpha of 0.05. Event rate in the control group was estimated as 40%, while that in the treated group was considered 5%. The number of resulting patients in each group is 19 for as total sample of 38 patients. This assumes a significant impact of treatment impact on S-IRIS-KS occurrence and its mortality.

The antiretroviral scheme will be assigned according to the criteria of the "The Antiretroviral Management Guide of Persons with HIV" in effect in Mexico.

Candidates will have an initial thorough clinical evaluation including a work-up to diagnose coinfections and rule out other neoplasms that comprise: ophthalmologic evaluation, computed tomography (CT) scan (neck, thorax, and abdomen), bone marrow culture with bone biopsy, Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) serology, venereal disease research laboratory (VDRL) test and if indicated lumbar puncture to rule-out neurosyphilis, Histoplasma urinary antigen and serology, and GenXpert MTB/RIF test. Upper gastrointestinal tract (GIT) endoscopy with biopsy of lesions; colonoscopy will be performed only on patients with diarrhea or lower-GIT bleeding. Biopsies of enlarged lymph nodes will be obtained and process for histopathological analysis and culture. If indicated, bronchoscopy with bronchoalveolar lavage (BAL) will be performed as well as a thoracic Gallium 67 Spect-CT Scan or PET-FDG scans.

Criteria for Non-severe-IRIS KS and Severe-IRIS-KS

Non-severe-IRIS-KS: Is defined as an increase in the number of KS lesions plus ≥one log10 of HIV-1 RNA VL decrease or ≥50 cells/mm3 or ≥2-fold from baseline CD4+ cells increase after cART initiation.

Severe-IRIS-KS: Is defined as an abrupt clinical deterioration after cART initiation alongside the presence of at least two clinical and at least three laboratory criteria.
Clinical criteria: 1) Fever (no identified concomitant infection), 2) increase in the size or number of KS lesions, 3) exacerbation of lymphedema, 4) appearance or increase of otherwise unexplained lung opacities on the chest images with a negative Gallium-Scan negative and 4) appearance or increase of pleural effusion.
Laboratory criteria: 1) Thrombocytopenia <100,000 platelets/ml; 2) Anemia (decrease of at least 1 g/dl from previous measure and no obvious bleeding), 3) Hyponatremia <135 mEq/L and 4) Hypoalbuminemia <3.5 g/dL. This is the clinical picture associated with death.

Classification of KS evolution:

Complete Response (CR): when all of the KS lesions disappear, according to physician´s criteria documented by pictures taken in each visit.
Partial Response (PR): when there was a diminution of >50% in number and/or size of original lesions without the appearance of new lesions, according to physician´s criteria documented by pictures taken in each visit.
Stable Disease (SD): was when there was a reduction of <50% of lesions and new lesions have not appeared, according to physician´s criteria documented by pictures taken in each visit.
Disease Progression (DP): when an increase is documented of the number and size of the KS lesions during follow-up periods.
Relapse: when new lesions appeared in patients with CR or documented CR in previous evaluations.

Visits will be performed at baseline, week 1, 2, 4, 8, 12, 16, 24, and 48. At each visit, an Infectious Diseases specialist will perform a clinical evaluation, and pictures of skin lesions will photograph. Blood samples will be obtained for: WBC count, complete blood chemistry, urine analysis, CRP, D-Dimer, HIV VL with Abbott Real-time, HHV-8, CMV, and Epstein-Barr Virus (EBV) VL ELITe MGB KIT by ELITe InGenius Software, CD4+ and CD8+ cells count and percentage, (flow cytometry, Facs Canto II, Becton Dickinson) CD4/CD8 ratio and plasma levels of interleukin 6, 10 (IL-6, IL-10), tumor necrosis factor (TNF) and interferon-gamma (IFN-ɣ) were measured using a sandwich-type immunoassay, ELISA (Biolegend). Serology for syphilis, HBV, and HCV will be repeated at week 24 and 48. If patients had an exacerbation of KS outside the scheduled visit they will be reevaluated with laboratory tests and study images.
A qualified phlebotomist will carry out blood sampling.

Primary outcome:
Mortality by all causes at end of follow-up, 48 weeks, adjusted at least by age, gender, CD4, and viral load of HHV-8, primarily with a survival analysis by a Cox regression, but also with a logistic regression model.

Secondary outcomes:
Total number of SIRI events (S-IRIS-KS and Non-S-IRIS-KS) in treated and control group. This is going to be done by a Poisson´s models analysis adjusted by age, gender, coinfections, basleine: CD4, and viral load of HV8, C reactive protein, HIV VL, IL6, IL10, TNF, and IFN. We will compare mortality in patients with pulmonary KS between groups.

Vigilance of adverse events:
Adverse events in treated and control group will be reported.

Statistical analysis:
The primary analysis is going to be as intention to treat, but as a secondary analysis also as per protocol analysis is going to be performed for mortality, and S-IRIS-KS.

Ethical issues:
Protocol and informed consent were reviewed and accepted by IRB form Instituto Nacional de Cancerología. (CEI/950/15No.15/03/INI)
First submission: 14 October 2014
First amendment: July 22, 2016
Second amendment. 25 April 2018