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Lay Abstract

Lymphoproliferative disorders are a type of lymphoma that develops in some transplant patients that can be progressive and fatal. Uncontrolled EBV infection in the setting of immunosuppression is thought lead to the development of post transplant lymphoproliferative disorders (PTLD). An antiviral medication, ganciclovir, has been associated with decreased rates of PTLD however this has not been studied in a randomized control trial. The hypothesis is that ganciclovir prevents primary EBV infection and therefore uncontrolled B cell proliferation and the subsequent development of PTLD. A multicenter double blinded placebo controlled trial will be conducted to study the incidence of PTLD in EBV negative transplant patients receiving ganciclovir vs. placebo. Procedures include phlebotomy for EBV & CMV antibody levels and possible biopsies in the diagnosis of PTLD. Ethic issues addressed include withholding prophylactic antivirals in transplant patients. Currently there is no standard of care for post transplant prophylaxis and patients may be offered the study drug if the patients have clinical or laboratory evidence of active CMV.

Study Purpose and Rationale

Lymphoproliferative disorders are among the most serious and potentially fatal complications of chronic immunosuppression in solid organ transplant recipients. Uncontrolled EBV driven B cell proliferation in the setting of immunosuppression post transplant has been implicated in the pathogenesis of posttranplant lymphoproliferative disorders (PTLD). The incidence of PTLD is approximately 1-10% in solid organ transplants and varies based on type of organ transplant. Major risk factors for the development of PTLD included degree of immunosuppression and EBV serostatus. Those most at risk are EBV negative recipients receiving EBV positive organs and it has been hypothesized that primary EBV infection precipitates post transplant lymphoproliferative disorder. As such, there has been much emphasis on therapeutic interventions to prevent primary EBV infection in these patients. A recent multicenter case control study performed in renal transplant patients has shown that antiviral therapy with ganciclovir reduced the risk of PTLD by up to 83% and much of that benefit was seen during the first year post transplant. The risk of PTLD was lowered by 38% for each 30 days of ganciclovir therapy (OR=0.62, 95% CI 0.38-1.0) Hypotheses have been made that ganciclovir may be effective at preventing PTLD because it works by prevention of the lytic phase of the viral life cycle during primary infection. The risk for the development of PTLD is highest in the first year post transplant making this the ideal time to study the development of primary infection and the development of PTLD.

Study Design and Statistical Analysis

A multicenter double blinded randomized control trial will be performed looking at the effect of prophylactic ganciclovir therapy on the incidence of PTLD in EBV seronegative patients. Subjects will be recruited from transplant centers across the United States.

Patients listed for transplant will be screened at their respective transplant clinics prior to transplant via EBV antibody testing and informed consent will be given by subjects prior to transplantation. During surgical transplantation, patients will be started on ganciclovir 1 g po tid or placebo and continued for 3 mo post transplant per current standard prophylactic recommendations. Patients will be followed for 3 years as rates of PTLD match that of the general population after this time period. The difference in incidence of PTLD will be analyzed in EBV negative patients who received ganciclovir vs those who did not receive ganciclovir prophylactically. If there appears to be a significant benefit from prophylactic ganciclovir, those patients randomized to the placebo group will be offered the drug as well. Physicians and patients will be blinded to ganciclovir status however if clinically indicated, physicians may be unblinded if there is suspicion for CMV disease and need for treatment with ganciclovir. Power will be calculated using Chi square testing with proportion of EBV negative patients with PTLD approaching that of the mean yearly incidence of 5% (1-10% range). The expected reduction in incidence of PTLD with the prophylactic use of ganciclovir is 80%. In order to achieve 80% power, 580 EBV negative transplant patients would need to be enrolled of which 290 would receive ganciclovir and 290 would receive placebo. Because 85% of the population is EBV positive, 3900 transplant patients would need to be screened to enroll 580 EBV negative patients. Chi square using a standard 2X2 table will be used to calculate p values of the incidence of PTLD in the two groups.

Study Procedures

Patients will have all necessary pre transplant blood work performed at their designated transplant centers. For the purposes of this study, EBV IgG and IgM levels as well as CMV IgG & IgM levels will be measured for baseline status. Post transplant, the above tests will be repeated at monthly intervals for the first year and then every 3 months for the next 2 yrs. If EBV antibody levels are positive, EBV viral load will be used as a confirmatory test. If CMV antibody levels are positive, PCR for viral load will be performed and if positive these patients may be unblinded and offered ganciclovir for treatment of CMV disease as is standard of care. In order to monitor for adverse affects of the study drug, monthly CBC and LFT testing will be performed monthly for the first 3 months as well. PTLD will be diagnosed by the study participants' primary physician. Criteria for the diagnosis of PTLD included the presence of a lymphoid tumor and two of three of the following criteria: disruption of underlying tissue architecture by a lymphoproliferative process, presence of mono or oligoclonal populations as determined by cellular or viral markers and EBV infection of many cells within the tumor. Tumor biopsies may be required for the diagnosis for PTLD.

Study Drug

Ganciclovir will be studied off label for the prevention of EBV induced PTLD. This is being studied based on several observational and case control studies showing reduced rates of PTLD in patients that received the drug. This however has not been studied in a randomized controlled manner. Although the mechanism of PTLD prevention is not

clear, ganciclovir requires phosphorylation to become active which happens during the lytic phase of the EBV viral life cycle. It is hypothesized that ganciclovir's potential efficacy may be due to the effect on the EBV lytic cycle of replication during infection. This therefore keeps the pool of EBV infected cells in control reducing the source of malignant B cells that lead to PTDL. Patients will receive induction therapy with 5 mg/kg IV q12h for 2 wks post transplant or placebo IVF followed by maintenance therapy with 1000 mg po tid for rest of the 3 month study period. These doses are based on standard of care for CMV prophylaxis and will be adjusted according to renal function. Patients may be continued on ganciclovir after the 3 mo trial period if clinically indicated. The major side effects of ganciclovir include anemia which can occur in 20-25% of patients, leucopenia 30-40%, abdominal complaints including pain, diarrhea, nausea 13-40%, rash 10-15% and fever 38-48%. Between 1-10% will experience headache, confusion, pruritus, thrombocytopenia & neutropenia. Less than 1% of patients will experience the following side effects: Alopecia, arrhythmia, ataxia, bronchospasm, coma, dyspnea, encephalopathy, eosinophilia, exfoliative dermatitis, extrapyramidal symptoms, hemorrhage, nervousness, pancytopenia, psychosis, renal failure, seizure, SIADH, Stevens-Johnson syndrome, torsade de pointes, urticaria, visual loss. Ganciclovir is contraindication in patients with hypersensitivity to ganciclovir, acyclovir, or any component of the formulation; absolute neutrophil count $<500/mm^3$; platelet count $<25,000/mm^{3.}$

Medical Device: none

Study Questionnaires: none

Study Subjects: Subjects aged 18-50 who are EBV seronegative and listed for transplant will be included. Exclusion criteria include patients less than 18 yrs of age, EBV seropositive status pre transplant, pregnant patients, patients with significant anemia, thrombocytopenia, leucopenia or transaminitis will also be excluded. Patients with any underlying psychosis will excluded due to the theoretic risk of neurologic complications from the study drug. Patients with hypersensitivity to ganciclovir, acyclovir, or any component of the formulation; absolute neutrophil count $<500/mm^3$; platelet count $<25,000/mm^3$ will also be excluded. EBV serostatus will be determined with EBV IgM and IgG levels drawn from peripheral blood pre transplant.

Recruitment of Subjects:

Subjects will be recruited from transplant centers across the US by their primary physician based on EBV seronegativity. The primary physician will determine whether individual patients are appropriate study subjects and will discuss the study with the patient prior to any communication with the research team.

Confidentiality of Study Data:

Each study participant will be assigned a unique identifying code and all other identifying information will be concealed to protect patient confidentiality. In the event the a patient's information requires decoding, for example in the cases of the diagnosis of CMV disease based on serology and patient's symptoms, the patient's primary physician will be notified that his/her patient has such test results so that they may be offered standard therapies.

Potential Conflict of Interest: none

Location of Study: Study will be conducted at multiple transplant centers across the US. The CUMC division of the study will be conducted at the transplant center of Columbia Presbyterian Hospital. Each institution's IRB will approve their individual participation in the study.

Potential Risks: The potential risks of receiving the study drug included but are not limited to anemia which can occur in 20-25% of patients, leucopenia 30-40%, abdominal complaints including pain, diarrhea, nausea 13-40%, rash 10-15% and fever 38-48%. Between 1-10% will experience headache, confusion, pruritus, thrombocytopenia & neutropenia. Less than 1% of patients will experience the following side effects: Alopecia, arrhythmia, ataxia, bronchospasm, coma, dyspnea, encephalopathy, eosinophilia, exfoliative dermatitis, extrapyramidal symptoms, hemorrhage, nervousness, pancytopenia, psychosis, renal failure, seizure, SIADH, Stevens-Johnson syndrome, torsade de pointes, urticaria, visual loss. Half of the participants will receive placebo instead of the treatment drug and therefore if there is a benefit of the treatment drug those receiving placebo will not benefit from it. If however, there appears to be a significant percentage of patients who receive benefit with the treatment drug, the trial may be stopped early and all patients will receive the treatment drug.

Potential Benefits: You may or may not benefit from participation in this study however information obtained by your participation in this study will help us obtain more information about possible preventative treatments for PTLD.

Alternative Therapies: There are no defined guidelines for prophylactic medications to prevent PTLD however some transplant centers have used acyclovir. Limited trial data indicates acyclovir may not be as effective as the treatment drug in this study. Some centers have also used immunoglobulin including IVIG and CMV specific immunoglobulin however there is currently no data available on their efficacy in prevention of PTLD. There is also the option of no therapy as you may not acquire EBV infection or PTLD after transplantation.

Compensation to Subjects: Patients will receive all study blood work and medications free of charge.

Cost to Subjects: none

Minors as Research Subjects: none

Radiation of Radioactive Substances: none

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