CLINICAL STUDY PROTOCOL

USM

UNIVERSITY SCHOOL OF MEDICINE

A Retrospective Review of the Primary Use of Immu[illegible]ppression in Cadaveric Liver Transplant Re[illegible]ients

Study Number

LIVHCC-2015

Sponsor

Samoht Institute of Transplantation

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Protocol Version

Version 1.0

November 10, 2015

Confidentiality Statement

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Synopsis

Primary Objective

The primary objective of the proposed study is to perform a retrospective review of approximately 400 liver transplant (Ltx) recipients to compare the efficacy of steroid-free immunosuppression (IS) regimen and induction IS regimen in liver transplant recipients with HCC.

Secondary Objectives (if applicable)

Secondary objectives of the proposed study include:

1. Compare the safety of steroid-free immunosuppression (IS) regimen and induction IS regimen in liver transplant recipients with HCC.
2. Compare specific data related to OS, rejection rates, and drug-related complications to the previously published data at other large academic transplant centers.

Primary Outcome Variables

The primary outcome variables will include: overall survival (OS), graft survival, and tumor-free survival.

Secondary Outcome Variables (if applicable)

To evaluate the secondary objective of safety the secondary outcome variables will include acute rejection rate and incidence of complications.

This study data will then be compared to the previously published data of other large academic liver transplant centers.

Study Duration

This retrospective chart review is expected to span 2 calendar years from the date of receiving IRB approval.

Study Design

This study will be a retrospective review of data from patients who underwent LTx at Samoht Institute of Transplantation between January 2004 - December 2014.

Study Population

This study will involve the review of medical records of patients with hepatocellular(Liver cells) carcinoma (HCC)(Hepatocellular carcinoma) that underwent a liver transplantation at the Samoht Institute of Transplantation during the 2004-2014. Patients who were pediatric (< 18 years of age), had undergone retransplantation, multiple organ transplantation, liver transplant for acute or fulminate liver failure, autoimmine hepatitis, and ABO(A B O) - incompatible liver transplantation, will not be included in this study.

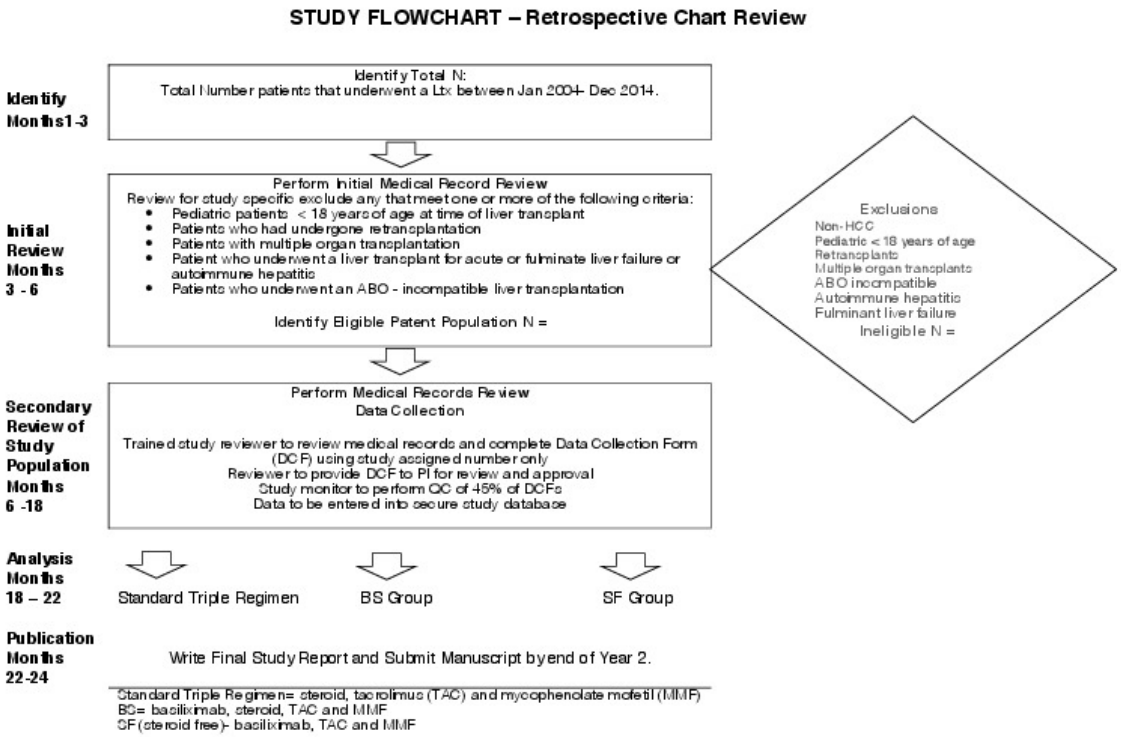
Number of Participants

It is estimated that approximately 900 medical records from patients who underwent liver transplantation will be reviewed for this study. It is estimated that 400 of these patients will meet inclusion criteria and be included in the study.

Number of Study Sites

This study will be conducted at one study site, the Samoht Institute of Transplantation at Alantis, Florida.

Study Flow Chart



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Abbreviations

Abbreviation	Definition
ABO	A B O
AFP	Alpha-fetoprotein
BMI	Body Mass Index
CMV	Cytomegalovirus
DCF	Data Collection Form
GCP	General Clinical Practices
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
IS	Immunosuppression
Ltx	Liver Transplant
OLT	Orthotopic liver transplantation
OS	Overall Survival
PI	Principal Investigator

Glossary of Terms

Glossary Term	Explanation
AFP	Alpha-fetoprotein Alpha-fetoprotein (AFP, α-fetoprotein; also sometimes called alpha-1-fetoprotein, alpha-fetoglobulin, or alpha fetal protein) is a protein that in humans is encoded by the AFP gene. The AFP gene is located on the q arm of chromosome 4 (4q25)

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1 Introductory Statement

1.1 Protocol Statement of Compliance

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP(General Clinical Practices) guidelines (CRF 21 Part 312), applicable government regulations and Institutional research policies and procedures.

2 Background

2.1 Background/prevalence of research topic

Liver cancer in adult men is the fifth most frequently diagnosed cancer worldwide, and is the second leading cause of cancer-related death in the world. [1] In adult women, it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death. In the United States (US), the annual incidence of hepatocellular carcinoma (HCC(Hepatocellular Carcinoma)) was at least 6 per 100,000 in 2010.[2] Among US children, the annual incidence was 0.05 cases per 100,000 in 2009.[3]

The number of deaths per year in HCC is virtually identical to the incidence throughout the world, underscoring the high case fatality rate of this aggressive disease. [1]

As a common malignancy worldwide, the incidence and mortality of hepatocellular carcinoma (HCC) varies widely with geographical region. Viral infection, mainly in chronic hepatitis B virus (HBV()) and/or hepatitis C virus (HCV()) infection, is the predominate cause of HCC globally. Almost 80 percent of all HCC cases are due to underlying chronic hepatitis B and C virus infection.[4]

Orthotopic liver transplantation (OLT()) is proved to be an efficient treatment to extend life for HCC patients with hepatitis virus infection. Immunosuppression (IS) plays a critical role in overall success of liver transplantation. The implementation of IS both pre and post surgery reduces the occurrence of both acute and chronic rejection, the most severe side effects after transplantation. Meanwhile the wide usage of IS brings some side effects. Evidence now indicates that a few of the long-term complications of liver transplantation (LTx) may be caused by IS side effects rather than chronic rejection, and it has been concluded that transplant recipients were being over immunosuppressed.[5]

It is hypothesized that patients who are strongly immunosuppressed may have several negative impacts including recurrence of HCC, as well as long-term

complications of diabetes mellitus, hypertension, osteoporosis, fractures and serious infections all adverse[4] effects of corticosteroid treatment.

3 Rationale/Significance

3.1 Problem Statement

There4 is a great need to optimize the success rate of liver transplantation in this country and worldwide, especially given the shortage of organs and the average wait time for a patient waiting liver transplantation.[6] In order to do this we must look to improve the post-transplant immunosuppression regimens.

3.2 Purpose of Study/Potential Impact

The purpose of the study is to conduct a retrospective review of liver transplants recipients and compare the efficacy and safety of immunosuppression regimens within our institution, in order that we may gain a better understanding as to how to make adjustments to drug dosing, drug combinations, drug withdrawal and addition of other immunosuppresants, so as to best optimize our liver transplant patients with HCC, and to share this information with the transplant community.

3.3 Potential Risks and Benefits

3.3.1 Potential Benefits

There are no direct benefits to the research subject. The research has the potential to improve the lives of future patients undergoing liver transplantation.

3.3.2 Potential Risks

There are no risks to the research subject as this is a retrospective review of medical records and no direct patient identifiers will be stored within the study database.

4 Study Objectives

4.1 Hypothesis

The hypothesis is that steroid-free IS regimens have higher rates of complications and are not more efficacious than the non-steroid IS regimens.

4.2 Primary Objective

The primary objective of the proposed study is to perform a retrospective review of approximately 400 liver transplant (Ltx)(Liver Transplant) recipients to compare the efficacy of steroid-free immunosuppression (IS) regimen and induction IS regimen in liver transplant recipients with HCC.

4.3 Secondary Objectives

Secondary objectives of the proposed study include:

1. Compare the safety of steroid-free immunosuppression (IS) regimen and induction IS regimen in liver transplant recipients with HCC.
2. Compare specific data related to OS, rejection rates, and drug-related complications to the previously published data at other large academic transplant centers.

5 Study Design

5.1 General Design

This study will be a retrospective review of data from patients who underwent LTx at Samoht Institute of Transplantation between January 2004 - December 2014. The study data to be collected will include data through the follow-up period up through December 2015.

5.1.1 Study Duration (if applicable)

This retrospective chart review is expected to span 2 calendar years from the date of receiving IRB approval.

Year 1, months 1-2, identify and obtain medical records of potential subjects.

Year 1, months 3-6, conduct initial review of medical records, for confirming eligible patient population collection of study specific data.

Year 1, months 6 - Year 2, month18, conduct thorough review of medical records, for collection of study specific data.

Year 1, months 18-20, perform initial analysis of data and re-review of medical records as needed.

Year 2, months 20-22, complete analysis of data, preparation of abstract for submission to meeting

Year 2, months 22-24, write manuscript and submit to journal.

5.1.2 Number of Study Sites

This study will be conducted at one study site, the Samoht Institute of Transplantation at Alantis, Florida.

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

In order to evaluate the primary objective, to compare the efficacy of steroid-free immunosuppression (IS) regimen and induction IS regimen in liver transplant recipients with HCC, the following primary outcome variables will be evaluated:

1. Overall survival (OS)(Overall Survival)
2. Graft Survival
3. Tumor-free survival

5.2.2 Secondary Outcome Variables (if applicable)

In order to evaluate the secondary objectives, to compare the safety of steroid-free immunosuppression (IS)regimen and induction IS regimen, the secondary outcome variables will include acute rejection rate and incidence of complications.

1. Compare specific data related to OS, rejection rates, and drug-related complications to the previously published data at other large academic transplant centers.

This study data will then be compared to the previously published data of other large academic liver transplant centers.

5.3 Study Population

This study will involve the review of medical records of patients with hepatocellular carcinoma (HCC)(Hepatocellular carcinoma) that underwent a liver transplantation at the Samoht Institute of Transplantation during the 2004-2014. Over 900 liver transplants were performed during this time and it is estimated from a prior completed pilot study to evaluate the feasibility of this review, that approximately 400 patients will meet the study criteria and will be included in the analysis of the primary objective.

5.3.1 Number of Participants

It is estimated that approximately 900 medical records from patients who underwent liver transplantation will be reviewed for this study. It is estimated that 400 of these patients will meet inclusion criteria and be included in the study.

5.3.2 Eligibility Criteria

The patient **must** meet the following criteria, in order for the patient's medical records and data to be included in the study:

Patients with sympotomatic HCC, or HCC reoccurence after primary liver resection who underwent a liver transplantation at the Samoht Institute of Transplantation during the period of January 2004 - December 2014.

Any patient the meets any one of the following criteria will be **excluded** from the study:

- Pediatric patients < 18 years of age at time of liver transplant
- Patients who had undergone retransplantation
- Patients with multiple organ transplantation
- Patient who underwent a liver transplant for acute or fulminate liver failure or autoimmine hepatitis
- Patients who underwent an ABO - incompatible liver transplantation

6 Methods

6.1 Data Collection

This is a retrospective chart review that will be conducted by trained study data abstractors. In order to ensure inter-rater reliability, at minimum 2 data abstractors will perform the data collection using a specific data collection form (see appendix 1) that defines the data points that will be collected and where in the medical record this information will be extracted. Data will be collected using a coded list and there will be no direct patient identifiers maintained in the study database. All computer data entry will be done using the assigned study identification number only.

The following data points will be collected:

- Gender
- Age at time of transplant
- Body Mass Index (BMI)

- Child-Pugh Score
- MELD Score
- Preoperative Cytomegalovirus (CMV) status
- Hepatitis B (HBV) and Hepatitis C (HCV) status
- Preoperative HBV and HCV viral loads
- Incidence of preoperative cirrhosis, pathology stage
- Incidence of preoperative diabetes mellitus
- Incidence of preoperative hypertension
- Prior treatment for HCC
- HCC TNM staging at time of diagnosis and at time of transplant
- Diameter of largest tumor in cm.
- Number of tumors
- Preoperative antiviral therapy
- Preoperative Alpha fetal protein levels (AFP)

6.2 Statistical Method

6.2.1 Sample Size Considerations

At minimum a total of 400 patient medical records will be reviewed for this retrospective chart review. This represent more than 10 cases per outcome variable being evaluated and therefore will be sufficient.

6.2.2 Planned Analysis

Continuous variables will be reported as mean and standard deviation or median and inter-quar- tile range (IQR) according to the distributions of variables. Categorical variables will be reported as frequencies and percentages. Kruskal-Wallis H test, chi square test or Fisher test were applied for univariate analysis. Life-tables and Kaplan-Meier analysis with log-rank test will be used for OS, graft and tumor-free survival analysis between different IS groups and survival curves were provided respectively. Cox proportional hazards regression analysis will be conducted for univariate and multivariate survival analysis to identify the predictors of survival. Crude and adjusted hazard ratios (HRs) with 95% confidence interval (CIs) will be reported. All statistical tests will be performed with 2-tailed $P<0.05$ indicating statistical significance and will be performed using software package SPSS 16.0

7 Trial Administration

7.1 Ethical Considerations

The study is a retrospective chart review and therefore does not pose any ethical issues as all data that will be used is already in existence and no additional study data will be included in the patient's permanent medical record.

7.2 Institutional Review Board (IRB) Review

The protocol, data collection form and relevant supporting information will be submitted to the IRB for review and must be approved before the study is initiated. The principal investigator is responsible for keeping the IRB apprised of the progress of the study, any changes made to the protocol, or any unanticipated problems. But in any the case the IRB must be updated at least once per year for the duration of the study.

7.3 Subject Confidentiality

Human subject's names will only be maintained on a list that will link direct patient identifiers to an assigned study identification number which will be kept by the Principal Investigator in a secure location with limited access for the duration of the study and maintained separate from the completed data collection forms (DCF). There will be no direct patient identifiers maintained in the study database. All computer data entry will be done using the assigned study identification number only. All data will be entered into a computer that is password protected. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the OHRP, the Sponsor, or the Sponsor's designee.

7.4 Unanticipated Problems

In the event that any unanticipated problems may occur in obtaining the number of medical records required to collect data for the analysis of the primary objective of the study, the Principal Investigator will notify the IRB and determine what action may be required.

7.5 Data Quality Assurance

This is a retrospective chart review that will be conducted by trained study data abstractors. The selected study data abstractors will be experienced in a health related field and training will be provided prior to the medical record review and data collection. Study specific training will include:

- Orientation to the paper and electronic based medical records
- Disease specific background information
- Detail review of the data collection form (DCF) that defines the data points that will be collected and where in the medical record this information will be extracted

In order to ensure inter-rater reliability, at minimum 2 data abstractors will perform the data collection and a monitor will perform random checks of the data collection.

Final review and sign off of each data collection form will be completed by the Principal Investigator, a transplant physician.

7.5.1 Data Collection

The process for data collection has been addressed under methods section for this chart review study.

7.5.1.1 Access to Source

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigators site and may include: hospital and clinic progress notes, discharge summaries, operative reports, copies of laboratory and medical test results, consent for procedures and operations, that exist in both the paper or electronic medical record.

Data transcribed in the DCF from the source document must be consistent with the source documents or discrepancies must be explained.

The investigator will permit trial related monitoring, audits, IRB review and regulatory inspection, providing direct access to all related source documents.

7.5.1.2 Data Storage/Security

The study's internet-based data entry system protects confidentiality and data security. Human subject's names will only be maintained on a hard copy list that will link direct patient identifiers to an assigned study identification number which will be kept by the Principal Investigator in a secure location with limited access for the duration of the study and maintained separate from the completed data collection forms (DCF) and the study database.

All computer data entry will be done on an internet-based data entry system (cloud storage), that is password protected and encrypted, and only the assigned study identification number will be associated with the data, there will be no direct patient identifiers stored within the study database.

7.6 Study Records

For the purposes of this study the following are considered study records and are to be maintained for the duration of the study and retained for the period as determined by the sponsor.

- Source documents including medical records, laboratory reports, medical test results, participant questionnaires, participant diaries, exercise logs
- Data Collection Forms (DCF)
- All IRB Correspondence, including initial submission, annual and continuing reports and any other submissions.

7.6.1 Retention of Records

All study records and documents pertaining to the conduct of the study including: Data Collection Forms, source documents, and IRB correspondence must be retained by the Principal investigator for 5 years following the completion of the study.

7.7 Study Monitoring

Data will be monitored by a study monitor prior to the data analysis. Any discrepancies noted between the DCF and the source documentation in the medical record will be resolved prior to data analysis.

7.8 Study Modification

All modifications to the study will only be made by the principal investigator. All protocol modifications will and must be submitted to the IRB for information and approval in accordance with local requirements. IRB approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to a study participant, or when changes involve only logistical or administrative aspects of the trial (change in telephone number, change in study staff- other than investigator).

7.9 Study Completion

The study completion will be defined as the completion of the data collection and the final analysis. The principal investigator will notify the IRB of the study completion.

7.10 Funding Source

This study is being funded and sponsored by the Samoht Institute of Transplantation.

7.11 Publication Plan

The sponsor shall retain ownership of all study data. All proposed publications based on this study must be subject to the sponsor's requirements and approval.

List of Tables

Title
Study Flowchart

References

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