Pharmacokinetics of doxorubicin in conventional transarterial chemoembolization (cTACE) of primary and secondary liver cancer

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Investigator Agreement Page

Study Title: Pharmacokinetics of doxorubicin in conventional transarterial chemoembolization (cTACE) of primary and secondary liver cancer

I confirm agreement to conduct the study in compliance with the protocol and all applicable regulations.

Investigator Name: _____

Affiliation: _____

Investigator Signature: _____ Date:_____

Log of protocol revisions –

Version 4/20/2017

- Change of principal investigator from Jeff Geschwind, MD to Todd Schlachter, MD
- Addition of Juan Carlos Perez Lozada, MD as co-investigator

Version 1/19/2017

- Modification of inclusion criteria #7 to only exclude previous chemoembolization to target area within 1 year.
- Addition of Rajasekhara Ayyagari, MD as co-investigator

Version 10/10/2016

- Addition of Jeff Pollak, MD as co-investigator
- Minor edits and revisions, the most significant being correction of inclusion criteria ECOG 0-2 to ECOG 0-1.

Version 6/22/2016

- Clarification of inclusion criteria #7 on page 8, 18
- Minor edits and revisions.
- Addition of co-investigators Hyun Kim, MD, and Todd Schlachter, MD
- Addition of research nurse Teresa White
- Addition of shipping information for PK samples

Schema/Synopsis

Name of Sponsor:

Principal Investigator: Todd Schlachter, MD (Investigator initiated)

Title of Study:

Pharmacokinetics of doxorubicin in conventional transarterial chemoembolization (cTACE) of primary and secondary liver cancer

Co-Investigators:

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Study Center:

Yale University School of Medicine

Anticipated Study Period (years):	**Phase of Development:**
July 2015 – August 2017 (2 years)	Phase I

Abstract:

Problem:

Conventional transarterial chemoembolization (cTACE) was the first type of TACE developed. cTACE consists of the injection of a mixture of chemotherapeutic drugs with Lipiodol, a contrast agent, followed by the injection of small beads to occlude the tumor feeding arteries. Despite the local injection of the chemotherapeutic drugs, pharmacokinetic (PK) studies of cTACE dating back to the 1990s demonstrated a high serum concentration peak of the chemotherapeutic drugs right after administration.

Research hypothesis:

This is not a hypothesis driven study. The purpose of this study is to perform a dedicated PK analysis of doxorubicin and its metabolite doxorubicinol after cTACE.

Importance of the research:

Newer forms of TACE that include drug eluting microsphere technology have been developed, with more favorable PK profiles than those found in the studies of cTACE which were performed several decades ago. The cTACE procedure has since matured, and in fact is now often administered selectively so that the chemotherapy can be delivered in close proximity to the tumor, rather than administered in a lobar or whole liver fashion. It is important to determine

the PK profile of the modern cTACE procedure in order to make comparisons with the newer forms of TACE. Finally, it is also important to know whether superselective cTACE results in less serum exposure of doxorubicin and doxorubicinol than when it is administered in a lobar non-selective manner. The findings may truly lead to a change in practice and a new set of technical guidelines.

Study Design:

Single site, prospective study, designed to measure PK of doxorubicin and its metabolite doxorubicinol at various timed intervals after cTACE in patients with primary or secondary liver cancer.

# of Patients (planned):

30 patients to be enrolled, approximately 15 patients with primary liver cancer and 15 patients with secondary liver cancer. Up to 40 patients may be consented if necessary in order to account for potential patients who screen-out or who are unable to complete sample collection for the PK (80% of planned draws). 15 patients will be assigned to the lobar treatment arm and 15 patients will be assigned to the superselective treatment arm.

Diagnosis and Main Criteria for Inclusion:

Patients with primary or secondary liver cancer that are recommended for cTACE and meet the inclusion/exclusion criteria.

Inclusion criteria:

1. Age ≥ 18 years.
2. Histologically, cytologically, or radiologically confirmed liver dominant or liver only malignancy.
3. Preserved liver function (Child-Pugh A-B class) without significant liver decompensation.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 at study entry.
5. Measurable or evaluable disease that will be directly treated with intrahepatic therapy (as defined by Response Evaluation Criteria in Solid Tumors [RECIST] 1.1).
6. Suitable for TACE based on blood parameters such as platelet count, bilirubin, and international normalized ratio.
7. May be enrolled with a history of prior liver directed chemoembolization if chemoembolization to the target lesion occurred > 1 year prior to enrollment date. TACE to different targets within 1 year prior to enrollment date, radioembolization to target location, or other form of intra-arterial therapy will not exclude subjects.

Exclusion criteria:

1. Serum total bilirubin > 3.0 mg/dL
2. Creatinine > 2.0 mg/dL
3. Platelets < 50000/µL
4. Complete portal vein thrombosis with reversal of flow
5. Ascites (trace ascites on imaging is acceptable)

Duration of treatment:

Patients are on study for 4 weeks, starting from the initial blood draw at baseline prior to the cTACE procedure until the last blood draw taken 3-4 weeks post-cTACE.

Statistical methods:

Primary outcome variable:

Pharmacokinetic profile of doxorubicin and doxorubicinol after cTACE

Pharmacokinetic parameters to be measured for each patient:

- Peak of the plasma concentration, time of maximum concentration, and area under the concentration-time curve (AUC).
- Pharmacokinetic profiles for each patient will be correlated with toxicity and tumor burden (size of target lesion), BSA, gender.
- PK profiles of lobar cTACE as compared to that of super-selective cTACE.

Secondary outcome variables:

1. **Feasibility**
   - Technical success of the cTACE procedure (technical failure is defined as the inability to administer the cTACE material, in which case the patient would be excluded from the study).
   - Dose of doxorubicin delivered.
2. **Safety**
   - All toxicities assessed as being at least possibly related, up to the 3-4 week follow-up visit (post cTACE) will be analyzed by descriptive statistics to show type, grade (NCI Common Toxicity Criteria v4.0), frequency, and time from cTACE.

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AUC	Area under concentration-time curve
CRF	Case report form
cTACE	Conventional transarterial chemoembolization
CTCAE	NIH Common Terminology Criteria for Adverse Events
DEB-TACE	Drug eluting bead transarterial chemoembolization
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group performance status
GCP	Good Clinical Practice
HCC	Hepatocellular carcinoma
ICH	International Conference on Harmonization
IRB	Institutional Review Board
NET	Neuroendocrine tumor
PET	Pancreatic endocrine tumor
PK	Pharmacokinetics
PRC	Protocol Review Committee
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
UPIRSOs	Unanticipated Problems Involving Risks to Subjects and Others

1. Introduction

1.1 Background/Rationale

Transarterial chemoembolization (TACE) is the combination of locally injected chemotherapy and embolization of the tumor feeding arteries. Due to good tumor response rates and a low incidence of side effects, this technique has evolved into the standard palliative treatment for a number of primary and secondary liver cancers, including hepatocellular, intrahepatic cholangiocellular, colorectal, and neuroendocrine cancer. Conventional TACE (cTACE), the first type of TACE developed, consists of the injection of a mixture of chemotherapeutic drugs with Lipiodol, an oil-based contrast agent, followed by the injection of small beads to occlude the tumor feeding arteries. Despite the local injection of the chemotherapeutic drugs, this technique was shown to result in a high serum concentration peak of the chemotherapeutic drugs right after injection. Drug-eluting beads were developed to release the chemotherapeutic agent over a longer period of time, resulting in a lower initial serum concentration and a higher concentration of the chemotherapeutic drug in the tumor treated area over time.

Since the development of drug-eluting beads, many research teams have focused on the advantages of Drug Eluting Bead TACE (DEB-TACE) over cTACE, including better tumor response and lower incidence of side-effects (1,2). Several PK studies comparing various bead types have been performed in different animal models (3-5). According to these studies, the serum concentration of chemotherapeutic drugs is lower using DEB-TACE compared to cTACE. However, the cTACE studies used for comparison date back to the 1990, at which time a variety of cTACE protocols were being used as the cTACE technique was still in its infancy. Over the years, several studies were performed to develop the optimal drug combination and delivery schema with regard to efficacy and toxicity (6, 7). To our knowledge, there is only a single, rather recent PK study comparing DEB-TACE to cTACE (8), however this study had only 5 patients in the c-TACE arm.

Thus, the purpose of this study is to perform a dedicated PK analysis of doxorubicin and its metabolite doxorubicinol after cTACE, and compare the PK profile of the two most widely used methods for cTACE, lobar and superselective.

1.2 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and represents more than 5% of all cancers. Approximately 500,000 cases of HCC are diagnosed each year and it is the third cause of cancer-related deaths (9, 10). There are wide geographical variations in the incidence of the disease with the highest rates in the developing countries of Asia and Africa. However, the incidence of HCC is increasing in North America and Europe (11).

Untreated HCC carries a poor prognosis and is directly related to degree of underlying cirrhosis and tumor stage. Early detection offers the only possibility for cure. Patient survival is generally not more than 6 months in patients with large tumor mass and advanced cirrhosis. Patients with small HCCs (<5cm diameter) and stable liver function have a better prognosis with 2-year survival rates of 56% (12).

HCC is now responsible for 14,000 deaths annually in the United States. It is generally accepted that surgical resection, liver transplantation, and percutaneous ablation are the only curative treatments for patients with early stage HCC. The shortage of donor livers further diminishes liver transplantation as a viable option for many patients. The majority of HCC patients (approximately 85-90%) are not candidates for curative treatments either due to poor liver function or the presence of advanced disease. These patients are treated with palliative treatments.

Chemotherapeutic agents (e.g. doxorubicin) can be infused directly into the systemic circulation but patients who receive this treatment suffer serious side effects that may be life threatening (e.g. cardiac toxicity), pain, nausea, vomiting, myelosuppression, and alopecia. For those patients able to receive systemic chemotherapy, response rates ranged from 15% to 20% and have had virtually no impact on survival.

These factors, combined with local pattern of disease dissemination, have made local interventional therapy the cornerstone of hepatocellular carcinoma treatment for unresectable disease and patients who are not eligible for treatment.

1.3 Hepatic Metastases from Solid Tumors

There are many solid-organ malignant tumors (colorectal carcinoma, neuroendocrine tumors, pancreatic endocrine tumors, and other non-colorectal non-neuroendocrine tumors) for which cure is not possible with current systemic agents. Many of these tumors are found to have already metastasized to the liver at the time of diagnosis or eventually metastasize to the liver despite best therapeutic efforts with available systemic agents. The liver is the most common site of metastases from colorectal carcinoma and is a frequent metastatic site for pancreatic endocrine tumors (PET), neuroendocrine tumors (NET), and other tumor types. Overall, the largest risk factor for the development of hepatic metastases is the stage of the primary tumor (colorectal carcinoma) or the size of the primary tumor (NET, PET). In hepatic metastatic disease, the most important prognostic factor is the percent of liver replaced by tumor. If allowed to grow and disseminate within the liver, metastatic deposits become the dominant, and often, the most life-threatening feature of the metastatic disease, either through progressive hepatic failure or production of excess endocrine products that produce potentially lethal systemic consequences (NET, PET).

Due to the relative sensitivity of the liver to radiation, external beam radiation has had limited utility in treating hepatic metastatic disease. Modest improvements have been achieved in the treatment of metastatic colorectal cancer using new combination regimens of systemic agents; however, most patients ultimately fail first-line therapy either based on lack of efficacy or inability to tolerate further courses of treatment (13). A number of new, non-radiation based liver-directed therapies have been developed for reducing or controlling tumor mass in the liver that have demonstrated varying efficacy and patient tolerance. These treatments also may produce serious morbidity that adversely impacts patient quality of life, and can result in life-threatening complications and adverse events.

In summary, the status of clinical managements of patients with metastatic disease involving the liver has experienced modest improvements over the past 40 years. Standardization of treatment approach has been hampered by the need to adapt therapy to tumor type and presentation, initial response to first line therapy and patient tolerance for therapeutic interventions. Diverse drugs, biologics, medical devices and surgical procedures are available for treatment of hepatic metastases. There is a clinical need to develop new, liver-directed therapies with less morbidity and improved patient tolerance compared with existing therapies. In addition, new therapies are needed that can be applied at any time in the ongoing course of treatment for a patient with metastatic liver disease.

1.4 Transarterial Chemoembolization for Hepatocellular Carcinoma and Metastatic Disease

Liver directed forms of therapy have become the mainstay of therapy for patients with unresectable HCC. These therapies include chemical (alcohol, acetic acid) and thermal (radiofrequency ablation, microwave, laser, etc) ablative techniques, as well as intra-arterial chemotherapy treatments. Intra-arterial therapies have been developed to take advantage of the fact that the hepatic artery supplies most of the blood flow and nutrients to hepatic tumors.

Of those, TACE is the most widely performed procedure for patients with unresectable HCC. Transarterial chemoembolization involves the periodic injection of a chemotherapeutic agent, mixed with an embolic material, into selected branches of the hepatic arteries feeding a liver tumor, thus combining chemotherapy administration with intra-tumor ischemia. The rationale for TACE is that the infusion of drugs such as doxorubicin, mitomycin-C, and cisplatin suspended in an oily medium followed by embolization of the blood vessel with embolic agents will reduce arterial blood supply to the tumor allowing greater delivery of the chemotherapy to the tumor and thus causing necrosis of the tumor. Lipiodol is the most common vehicle used for the intra-arterial administration of the chemotherapeutic agents. The advantage of TACE is that higher concentrations of the drug can be delivered to the tumor with decreased systemic exposure compared with systemic chemotherapy. TACE has been shown to deliver up to 400 times the

intra-hepatic concentration of chemotherapy in comparison to intravenous administration depending on the chemotherapeutic agent (14). As such, tissue levels of chemotherapy within the tumor were found to be 40 times of that found in surrounding normal hepatic tissue. Embolization of a branch of the hepatic artery after the administration of chemotherapy results in the detection of the chemotherapeutic agent within the tumor of upwards of several months post administration (15-17).

TACE achieves partial response in 15-55% of patients (18-24) and significantly delays tumor progression and vascular invasion (20, 24). Two studies have also reported survival benefits for chemoembolization in selected patients (24, 25). The best candidates for chemoembolization are those with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread.

The impact of TACE on survival has been assessed through numerous prospective and retrospective studies. Two recently published randomized prospective clinical trials have shown a statistically significant survival advantage for TACE compared to symptomatic treatment. The first trial, which utilized cisplatin, Lipiodol, and gelatin sponge particles in 80 Asian patients, showed one-, two- and three-year survival rates of 57%, 31%, and 26% in treated patients compared to 32%, 11%, and 3% (respectively) in control patients treated with best available supportive care, giving a relative risk of death of 0.49 (CI, 0.29-0.81) (26). A second trial performed in Europe also showed a survival benefit in highly selected patients using Lipiodol, doxorubicin, and gel foam (23). A recent meta-analysis published by Llovet and Lo confirmed the findings of the two randomized trials and showed that chemoembolization provides significant survival benefit in a selected group of patients, namely those with good performance status (22). Based on those and other studies, chemoembolization is currently the standard of care for patients with intermediate stage HCC and has been included since 2006 as part of the official guidelines for the treatment of patients with HCC (by the American Association for the Study of Liver Diseases (AASLD), as well as the National Cancer Care Network (NCCN) and European Association of the Study of the Liver (EASL). TACE has also been used with success in secondary unresectable hepatic malignancies.

1.5 Lobar and Superselective TACE

The lobar conventional TACE approach consists of the administration of chemotherapy and Lipiodol to via the left or right hepatic lobar branch followed by embolization. As a consequence of this approach, a large region of the liver is treated which would make it suitable for cases where there are multiple lesions within a lobe. However, this technique was also correlated to a high serum concentration of the chemotherapeutic drug after administration, which compared unfavorably to an alternate form of treatment, the drug-eluting bead TACE (DEBTACE).

While the lobar technique is still very much in use today, TACE protocols have been refined and new specialized protocols developed. The superselective approach would advance the microcatheter further into the hepatic arterial branch afferent to the segment in which the tumor is located, or if possible the tip of the catheter will be further advanced into the subsegmental branches feeding the tumor, where chemotherapy will be administered followed by embolization. In this manner, the chemotherapy is delivered in a more selective fashion, sparing more of the healthy liver parenchyma.

Logistically, the superselective approach introduces new complexities including a lengthier operation and being more technically demanding, but some studies have observed that the superselective approach may result a higher rate of complete tumor necrosis with small HCCs in comparison to the lobar approach (27-29). In Golfieri's study, tumor necrosis was greater in the superselective arm vs the lobar arm (75.1% vs 52.8%), and complete tumor necrosis was observed in approximately two times more patients on the selective arm when compared to the lobar nonselective arm, which also resulted in a reduced need for further treatments (27). The damage to liver parenchyma and function was also reduced with the superselective approach, with less adverse events when compared to the nonselective TACE (28). A superselective or subsegmental approach could also be performed in patients who may be contraindicated for conventional nonselective TACE due to severe cirrhosis and risk of serious ischemic complications (30, 31). Given the reduced adverse event profile of the subsegmental approach and the selective nature of treatment, it is conjectured that the serum doxorubicin concentration would also be decreased.

1.6 Transarterial Chemoembolization Safety Profile

Generally, TACE is a well-tolerated procedure, although side effects are common. Embolization of the liver has been performed for decades for a variety of indications and is well-tolerated. Embolization of solid organs causes a self-limited post-embolization syndrome in the majority of patients, consisting of varying degrees of pain, nausea, vomiting, and fever. This is independent of chemotherapeutic drug use, reason for embolization (e.g. bleeding, tumor), and the organ treated (e.g. liver, kidney, spleen, uterus). With current medical care (e.g. hydration, anti-emetic therapy, and pain control), post-embolization syndrome is well-tolerated and 50% of patients can be discharged from the hospital the day after chemoembolization. The average length of stay is 1.5 days. Liver function is transiently affected with an increase in liver aminotransferase levels. These values usually peak 3-5 days after therapy and return to baseline levels by 10-14 days after embolization. There is no sustained degradation of liver function in properly selected patients who do not meet the well-established exclusion criteria for hepatic artery occlusion, even in the presence of cirrhosis (32). Because most of the injected drug is retained in the liver, systemic toxicity is minimized, with little bone marrow

suppression. The cumulative toxicity is far more limited than is experienced with systemic chemotherapy, which requires protracted drug exposure for an indefinite period of time. Treatment related complications occur in approximately 10% of performed procedures, with mortality rate around 2% (33).

Serious adverse events occur after approximately 5% of chemoembolization procedures. The most common serious adverse events are liver abscess or liver infarction, which occur in approximately 2% of cases each. The 30-day mortality rate is 1% (34-36) (37).

Constitutional symptoms: The post embolization syndrome consisting of transient abdominal pain, ileus, fever and malaise affects 60% to 80% of patients receiving TACE. Prophylactic antibiotics are not routinely administered as the fever is a predictor of treatment response. This fever is a result of tumor necrosis initiated by the therapy.

Gastrointestinal side effects and complications: Transaminases commonly rise 10 fold. Patients may develop ischemic cholecystitis, hepatic abscess, or biliary strictures. Additionally, a minority of patients will develop nausea/vomiting and ascites.

Endocrine complications: Some patients may develop symptomatic hypothyroidism as a result of retained iodine load.

Hematologic complications: Some patients may develop a leukemoid reaction. Bone marrow toxicity is uncommon occurring in less than 4% of patients and includes neutropenia and thrombocytopenia. A small cohort of patients has developed gastrointestinal hemorrhage as a result of TACE therapy.

2. Study Objectives and Endpoints

2.1 Primary Objectives/Endpoints

Doxorubicin pharmacokinetics will be performed on all 30 patients. Peripheral blood will be sampled for doxorubicin concentrations just before the cTACE procedure at baseline, and then after cTACE at the following time points: 5 minutes, 10 minutes, 20 minutes, 40 minutes, 1 hour, 2 hours, 4 hours, 24 hours, and 3 or 4 weeks post cTACE. This will be used to construct a pharmacokinetic profile of doxorubicin/doxorubicinol to include:

- Parameters of PK analysis including peak of the plasma concentration (C_{max}), time of maximum concentration, and area under the concentration time-curve (AUC).
- PK profiles for each patient will be correlated with toxicity and tumor burden (size of target lesion), BSA and gender.
- Comparison of PK profile between lobar administration and superselective administration.

2.2 Secondary Objectives/Endpoints

Feasibility:

- Technical success of the cTACE procedure (technical failure is defined as the inability to administer the cTACE material, in which case the patient would be excluded from the study)
- Dose of doxorubicin delivered

Safety:

- All toxicities assessed as being at least possibly related, up to the 3-4 week follow-up visit (post cTACE) will be collected. Toxicities will be analyzed by descriptive statistics to show type, grade (NCI Common Toxicity Criteria v4.0), frequency and time from cTACE.

3. Subject Selection

3.1 Subject Selection

Patients must have histologically, cytologically, or radiologically confirmed liver dominant or liver only malignancy. Patients must have an ECOG performance status of 0-1 at study entry and maintain a Child-Pugh class of A-B without significant liver decompensation (see Tables below). There must be measurable or evaluable disease that will be directly treated with intrahepatic therapy (as defined by Response Evaluation Criteria in Solid Tumors [RECIST] 1.1).

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Death

ECOG Performance Status: describes a patient's functional level in terms of self-care and physical activity.

Parameter	Points Assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	≤ 2	2-3	> 3
Albumin, G/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin Time			
Seconds over control	1-3	4-6	> 6
INR	< 1.7	1.8-2.3	> 2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Child-Pugh Classification of Liver Disease Severity: Modified Child-Pugh classification of liver disease severity according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one-year and two-year percent survival; grade A – 100 and 85 percent; grade B – 80 and 60 percent; and grade C – 45 and 35 percent, respectively.

3.2 Inclusion Criteria

Inclusion criteria as follows:

1. Patient's age is ≥ 18 years.
2. Histologically, cytologically, or radiologically confirmed liver dominant or liver only malignancy.
3. Preserved liver function (Child-Pugh A-B class) without significant liver decompensation.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 at study entry.
5. Measurable or evaluable disease that will be directly treated with intrahepatic therapy (as defined by Response Evaluation Criteria in Solid Tumors [RECIST] 1.1).

6. Suitable for TACE, based on blood parameters such as platelet count, bilirubin, and international normalized ratio.
7. May be enrolled with a history of prior liver directed chemoembolization if chemoembolization to the target lesion occurred > 1 year prior to enrollment date. TACE to different targets within 1 year prior to enrollment date, radioembolization to target location, or other form of intra-arterial therapy will not exclude subjects.

3.3 Exclusion Criteria

Exclusion criteria as follows:

1. Serum total bilirubin > 3.0 mg/dL.
2. Creatinine > 2.0 mg/dL
3. Platelets < 50000/µL
4. Complete portal vein thrombosis with reversal of flow.
5. Ascites (trace ascites on imaging is acceptable).

3.4 Inclusion of Women and Minorities

All patients, regardless of sex or ethnicity, presenting for cTACE for primary or secondary liver cancer will be reviewed for study eligibility. For participants who are not fluent in spoken or written English, interpreter services will be available both during the informed consent process and during the subject's participation as needed. A translated short form consent will be provided.

4. Subject Registration Procedures

4.1 General Guidelines

All patients would be seen for an initial visit at the Interventional Radiology clinics, where a clinician would present all treatment options. If the patient expresses an interest in the study, a member of the study team designated to consent patients would discuss the protocol in greater detail explaining the risks and benefits of the study, and obtain informed consent from the patient or a legally acceptable representative. Imaging, laboratory results, and medical history will be used as part of the screening process to determine the patient's eligibility for the study.

4.2 Registration Process

Patients consented for the study will be registered with OnCore, Yale's Clinical Trials Management System, and be assigned a study identifier and counted for the final data analysis. Patients' progress while on the study will be managed via OnCore.

4.3 Screening Assessments

Assessment completed in the initial clinic visits (pre-consent), as part of standard of care assessments, may be used as part of the study screening assessment.

- Detailed medical history including previous cancer history and cancer treatment. Any additional relevant medication taken one year prior to study start will also be recorded.
- History and physical exam (including vital signs, ECOG-PS assessment, height, weight) within 30 days of cTACE.
- Chemistry panel: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (total and direct), alkaline phosphatase (AP), total protein, albumin, calcium, phosphate, glucose, creatinine, blood urea nitrogen (BUN).
- Electrolyte panel: sodium, potassium, chloride.
- Complete blood count: hemoglobin, hematocrit, platelet count, white blood cell count (WBC). WBC should include differential neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts.
- Prothrombin time and INR.
- Appropriate tumor marker: alpha feto-protein (AFP), carcinoembryonic antigen (CEA), CA 19-9, etc.
- Serum or urine pregnancy test for women of childbearing potential (must be negative)
- Contrast enhanced MRI of the liver within 30 days of treatment. A CT may be used if a MRI would be improbable to obtain.

5. Study Design/Investigational Plan

5.1 Overall Design

The study is a single site, prospective study, designed to measure the PK of doxorubicin and its metabolite doxorubicinol at various timed intervals after cTACE in patients with primary or metastatic liver cancer.

Up to 30 patients will be enrolled that meet study entry criteria; approximately 15 with primary liver cancer and 15 with secondary liver cancer. Up to 40 patients may be consented if necessary in order to enroll these 30 patients, to account for potential patients who screen-out or who are unable to complete sample collection for the PK (80% of planned draws). 15 patients will be enrolled into the lobar cTACE arm and 15 patients will be enrolled into the superselective cTACE arm. The assignment of the treatment arm will be determined by the PI or a designated radiologist after review of the patient's imaging and history.

The study is planned to complete enrollment in two years, with another month to conclude patient follow-up.

5.1.1 Routine Care Procedures

Patients will undergo cTACE according to the standard of care hospital protocol. Depending on the assigned treatment arm, a lobar or superselective cTACE procedure will be performed.

To perform the superselective TACE technique, the tumor-feeding arteries will be catheterized with a coaxial microcatheter passed through a 5-Fr catheter previously placed either the right or left hepatic artery. The tip of the microcatheter will be placed into the hepatic arterial branch afferent to the segment in which the tumor is located, or if possible the tip of the catheter will be further advanced into the subsegmental branches feeding the tumor. After the microcatheter placement, the chemotherapy mixture will be injected under fluoroscopy, followed by injection of 1% lidocaine and 100-300 micron embospheres.

Nonselective lobar TACE will consist of injection of the same chemotherapy materials used in the superselective procedures into the right or left lobar branches.

The amount of chemoembolization material administered is titrated to the area being treated, i.e., a smaller area (lesion) may be adequately treated with a portion of the prepared chemoembolization material. The chemoembolization material consists of 10cc of chemotherapy, with 50 mg doxorubicin and 10 mg of mitomycin-C mixed 1:1 with Lipiodol (approximately 10cc) giving a total of approximately 20cc. After the chemotherapy is administered, approximately 10cc of 1% lidocaine and 1-2 vials of embospheres measuring 100-300 microns are injected. The amount of 1% lidocaine and embospheres is titrated to each clinical situation.

Intra-arterial chemotherapy materials:

- 10 cc of chemotherapy, with 50 mg doxorubicin and 10 mg of mitomycin-C mixed 1:1 with Lipiodol (approximately 10cc) giving a total of approximately 20 cc.
- 10 cc of 1% lidocaine
- 1-2 vials of embospheres measuring 100-300 microns to achieve angiographic end-point of 2-5 heart beats to clear the contrast column.

Following the chemoembolization procedure, the patient is admitted for observation, pain control, and hydration, and is discharged home once they are stable. The day after the TACE procedure, a non-contrast CT scan is performed to document the deposition of the Lipiodol.

Follow-up imaging, labs, and clinical assessment are done 3-4 weeks following the cTACE procedure.

5.1.2 Research Procedures

Based on previous methodology utilized in our research trial J1306 at Johns Hopkins and other TACE trials, venous blood will be sampled for doxorubicin concentrations just before the cTACE (pre-) and then repeatedly after cTACE at the following time points: 5 minutes, 10 minutes, 20 minutes, 40 minutes, 1 hour, 2 hours, 4 hours, 24 hours, and 3-4 weeks post cTACE. Data will be collected and recorded on the Doxorubicin PK Worksheet.

Instructions for processing PK samples:

> Blood samples will be collected in a heparinized tube (6 mL) from subjects at the time points on the study collection calendars (baseline, 5, 10, 20, 40 min, 1, 2, 4, 24 hours, 3-4 weeks). Blood samples will be centrifuged at 1000x g (or 3000 rpm) for 10 minutes at 4^{o}C and stored frozen at -20^{o}C or below until analyzed. The samples will be analyzed for total plasma doxorubicin and doxorubicinol at the Analytical Pharmacology Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.

Shipment of PK samples:

Samples will be kept at the study site and periodically during the study shipped to the APC Laboratory. Unless otherwise stated, samples will be shipped to the Johns Hopkins SKCCC Analytical Pharmacology Core (APC) Laboratory under the direction of Michelle A. Rudek, Pharm.D., Ph.D. Specimens should be stored through the duration of the PK study and shipped as a batch. A participant's samples should be shipped to the APC lab within 3 months of the last sample's collection date. (i.e., if C1D1 sample is collected on 1/1/2016, all of the participant's samples should be at the APC lab by 4/1/2016). If another set of participant samples can be batched by waiting up to 2 weeks (i.e., 3.5. months), this deviation is allowed.

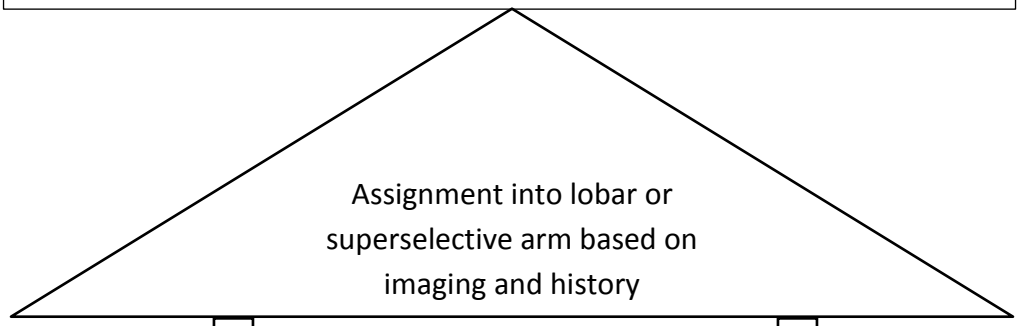
Samples will be shipped with a copy of the Doxorubicin PK Worksheet to the APC laboratory. Overnight shipments should occur on **Monday** through **Wednesday** (**Tuesday** is the preferred day) except when the following day is a holiday. A fax or call should be placed to the Analytical Pharmacology Core Laboratory prior to shipment providing the shipment tracking information. Samples should be shipped on dry ice to:

Analytical Pharmacology Core Laboratory
Attn: Geschwind/Schlachter cTACE doxorubicin Study Samples
1650 Orleans St. CRB1 Rm 184
Baltimore, MD 21231-1000
Phone: 410-502-7192 or 410-955-1129
Fax: 410-502-0895

5.2 Visit Schedule and Study Evaluation

Screening

Total 30 patients (up to 40 consented), approximately 15 with HCC and 15 with secondary liver cancer (range: 8-20): Obtain informed consent, screen potentials subjects by inclusion and exclusion criteria, register eligible participants, obtain MRI imaging and labwork if not already completed.



Lobar arm:
15 subjects (8-20)

Superselective arm:
15 subjects (8-20)

Day 0

PK baseline blood draw performed prior to cTACE.

cTACE procedure, lobar vs superselective approach as assigned.

PK blood draws at: 5, 10, 20, 40 min, 1, 2, 4 hours after cTACE.

Day 1

PK blood draw 24 hours after cTACE.

Standard of care non-contrast abdomen CT to ensure Lipiodol administration.

Day 21-28

Standard of care clinical followup, H&P, labwork, MRI or CT imaging.

PK blood draw at 3-4 weeks.

Please see appendices for additional study calendar.

5.3 Duration of Therapy

There will be one cTACE procedure performed at baseline, done as standard of care. PK blood sampling will continue until the 3-4 week time point.

5.4 Duration of Follow-up

Patients will return 3-4 weeks after the cTACE for clinic visit, H&P, laboratory tests, and new imaging as part of standard of care. The final PK blood sample will be drawn at this time.

5.5 Criteria for Removal from Study

A study participant may be removed from the study for any of the following reasons:

- At the request of the patient or a representative, i.e., withdrawal of consent.
- Patient falls out of eligibility criteria
- Technical failure of the cTACE procedure
- Use of illicit drugs or other substances that may, in the opinion of the investigator, contribute to toxicity
- The patient is lost to follow-up
- Death

6. Adverse Event Collection and Reporting Requirements

6.1 Definitions

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding, for example), symptom, or disease temporally associated with the treatment.

A Serious AE (SAE) is an untoward medical occurrence that at any dose produces any of the following outcomes:

- Results in death;
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe):

- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below for exceptions);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

NOTE:

The following hospitalizations are not considered SAEs:

- Admissions as per protocol for a planned medical/surgical procedure;
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy);
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases;
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

6.2 Adverse Event Coding

CTCAE term (AE description) and grade: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all AE reporting.

6.3 Adverse Event Capture and Reporting

Risks associated with the research procedures are expected to be minimal, and are involved with the drawing of blood and the placement of the IV catheter (second sheath). They include pain, bruising, swelling and bleeding when the catheter is placed. There is also a risk of infection at the IV site, and very rarely, nerve damage.

Adverse Events are collected through 3-4 weeks post cTACE and documented for each patient on the AE case report form (CRF). The AEs are transcribed onto a study-specific electronic AE log which is reviewed regularly by the PI and is available for the IRB and monitoring committees for review.

Study deviations (protocol deviations: PDs) are collected and reported in the same way as the AEs are managed. PDs are collected through 3-4 weeks post cTACE, and documented on CRFs and into PD electronic logs, which are reviewed regularly by the PI and available for IRB and monitoring committees for review.

Unanticipated Problems Involving Risks to Subjects and Others (UPIRSOs) that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project via email as they are reviewed by the PI. The Cancer Center Protocol Review Committee (PRC), Yale Cancer Center Data and Safety Monitoring Committee (DSMC), study sponsor, funding and regulatory agencies will be informed of serious adverse events within 5 days of the event becoming known to the Principal Investigator.

7. Statistical Methods

7.1 Primary Outcome Variable

Pharmacokinetic profile of doxorubicin and doxorubicinol after cTACE for each patient:

- Parameters of PK analysis including peak of the plasma concentration (C_{max}), time of maximum concentration, and area under the concentration time-curve (AUC).
- PK profiles for each patient will be correlated with toxicity and tumor burden (size of target lesion), BSA and gender.
- Comparison of PK profile between lobar administration and superselective administration.

7.2 Secondary Outcome Variables

Feasibility:

- Technical success of the cTACE procedure (technical failure is defined as the inability to administer the cTACE material, in which case the patient would be excluded from the study)
- Dose of doxorubicin delivered

Safety:

- All toxicities assessed as being at least possibly related, up to the 3-4 week follow-up visit (post cTACE) will be collected. Toxicities will be analyzed by descriptive statistics to show type, grade (NCI Common Toxicity Criteria v4.0), frequency and time from cTACE.

7.3 Statistical Plan

Up to 40 patients may be consented in order to enroll 30 patients, and to account for patients who are unable to complete sample collection for the PK (80% of planned draws). 15 patients will be enrolled into the lobar cTACE arm and 15 patients will be enrolled into the superselective cTACE arm.

We have assumed a clinically significant change in doxorubicin exposure would be 50%. In order to have 80% power to detect a 50% change with a 5% α, the sample size varies depending on the variability noted with TACE therapy. In the Varella trial utilizing cTACE with a Lipiodol doxorubicin formulation, the variability was reported as 30% Coefficient of Variation (CV). In our recent trial (J1306) utilizing TACE with a Drug Eluting Bead (DEB) doxorubicin formulation, the variability was reported as 90% CV. We anticipate the Lipiodol formulation to behave more like the Varella trial with 15 patients allowing for slightly higher variability.

***%CV**	**30%**	**43%**	**90%**
Expected Sample Size	**8**	**15**	**58**

*Methodology/calculator accessed from the websites below on 11/6/2014:
https://www.statstodo.com/SSizBioequiv_Tab.php
https://www.statstodo.com/SSizBioequiv_Pgm.php#

Continuous variables will be reported as means and standard deviations, medians and ranges, or both. Categorical variables will be reported as numbers and percentages. Pharmacokinetic parameters will be calculated by standard noncompartmental methods using Phoenix WinNonlin 6.1 (Pharsight, Mountain View, CA) for each patient. Pharmacokinetic parameters will be summarized using descriptive statistics.

Comparisons of the pharmacokinetic profiles between the lobar cTACE group and the superselective cTACE group will be performed using the Mann-Whitney U test. Correlations between pharmacokinetic profiles and clinical toxicities will be performed using the Kruskal-Wallis one-way ANOVA test. Correlations between the pharmacokinetic profiles and tumor burden will be performed with the Spearman's correlation coefficient. A P value < 0.05 will be considered statistically significant in all cases.

Interim analysis:
After the 16th patient has completed the study, including approximately 8 in each cTACE arm, the PK parameters will be measured for each patient in order to formally review the accumulated data and to inform the investigators whether any protocol modifications need to be made.

7.4 Early Stopping Rules

Not applicable for this study.

8. Regulatory Considerations

8.1 Data and Safety Monitoring Plan

This study is expected to be of minimal risk, and as such, will follow the guidelines for a minimal risk DSMP. The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. An internal monitoring plan will be established with the YCC to facilitate this process, and the study will be reviewed annually at minimum.

The principal investigator, the Institutional Review Board (IRB), Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects and Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project via email as they are reviewed by the PI. The Cancer Center Protocol Review Committee (PRC), Yale Cancer Center Data and Safety Monitoring Committee (DSMC), study sponsor, funding and regulatory agencies will be informed of serious adverse events within 5 days of the event becoming known to the principal investigator.

8.2 Case Report Forms

As used in this protocol, the term case report form (CRF) refers to a paper form. A CRF is required and should be completed for each included subject.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms.

All CRFs must be signed by the investigator to verify that the data contained on the CRFs is accurate. Any corrections to entries made in the CRFs and source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

Usually, source documents are the hospital's or the physician's subject medical chart. In these instances the data collected on the CRFs must match the data in the corresponding charts. A CRF, or part of the CRF, may also serve as a source document.

Electronic master logs of all adverse events and protocol deviations will also be recorded and kept in an encrypted database with access only available to study team members. An individual physical paper CRF will also be kept with the patient's research binder.

8.3 Record Retention

To enable inspections and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (i.e. information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the IRB's policies or the FDA's regulations, whichever is longer but for a minimum of 5 years.

If the investigator is unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the study records must be transferred to a designee acceptable to the investigator such as another investigator or another institution.

9. Ethics

9.1 Institutional Review Board (IRB)

It is the responsibility of the investigator/sponsor to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB. All IRB correspondence should be retained in the Investigator File.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996). In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

9.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any reports, publications, or in any other disclosures, except where required by laws.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form must be used in this study, and any changes made during the course of the study must be prospectively approved by the IRB before implementation.

The investigator must ensure that each subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

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11. Appendices

Study Visit Calendar

	Day -30 to 0	Day 0 (baseline)	Day 1	Day 21-28
Informed consent	X			
I/E criteria	X			
Medical history, H&P	X			X
Serum/urine pregnancy test (if applicable)	X			
Blood chemistry, hematology/coagulation	X			X
Tumor marker: AFP, CEA, CA 19-9, etc.	X			X
MRI scan, contrast enhanced of the liver	X			X
cTACE procedure		X		
Doxorubicin PK*		X	X	X
Non-contrast CT abdomen (standard of care)			X	

*PK blood samples will be drawn at: baseline (pre-cTACE), 5, 10, 20, 40 min, 1, 2, 4, 24 hours, and at 3-4 week time points after cTACE.