THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Clinical and technical feasibility of a ultrasuperparamagnetic nanoparticle iron oxide (USPIO)-enhanced magnetic resonance lymph node imaging
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Core Protocol Information

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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Background

The accurate nodal staging at the time of initial presentation or during the surveillance of oncologic patients is important in treatment planning and predicting the clinical outcome. Some of these nodes are not easily accessible for tissue diagnosis. The accuracy of the current imaging techniques detecting metastatic nodal disease are, however, notoriously suboptimal and vary greatly depending on the criteria [1-7].

An ultra-small superparamagnetic nanoparticle iron oxide, Combidex® (ferumoxtran-10), has shown promising results in evaluating the lymph nodes in patients with several different solid tumors and locations [8-14]. One of the largest series from Massachusetts General Hospital has shown about 90% sensitivity and 98% specificity in diagnosing the metastatic pelvic lymph nodes in patients with prostate carcinomas with 41% sensitivity and 98% specificity for the nodes less than 5 mm [14]. Our preliminary work using the Combidex® has shown technical feasibility (unpublished data) (Fig 1). This MR imaging contrast, however, is no longer manufactured. Recently a similar superparamagnetic nanoparticle, Feraheme® (ferumoxytol) has been FDA-approved as an iron replacement product in treatment of the iron deficiency anemia in an injectable solution [15]. These two agents are very similar in their size and pharmacokinetics (Table 1) [15, 16]. Once ferumoxytol is injected, like ferumoxtran-10, the colloids are taken by macrophages in RES system, including the liver, spleen and bone marrow. Once it enters the hepatocyte, it breaks down to release the iron. It reaches the nodes within 1-2 days and stays longer than 7 days [15, 16].

These USPIO particles or macrophages, when they reach the reticular endothelial system, such as liver or lymph nodes, create microscopic field gradients resulting in predominant susceptibility effect and generate local field inhomogeneity promoting dephasing the proton spins and increasing proton relaxation rates, which reduces the tissue T2 values. This results in homogenous and significant decrease in signal intensity (SI) on T2 and T2*-weighted images on MRI [17-19].

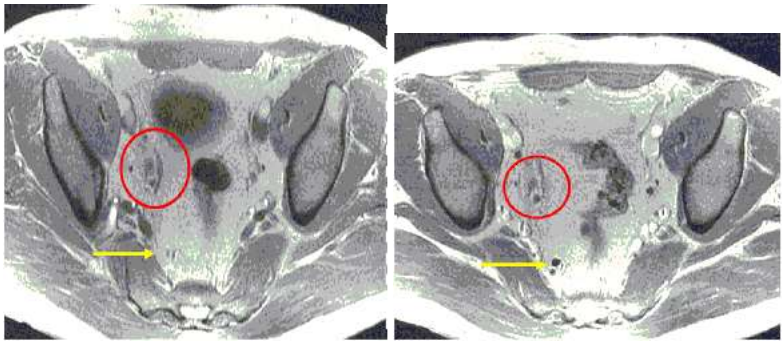

Figure 1. Pre- (a) and 24-hour post (b)-Combidex® enhanced T1-weighted images in a patient with bladder cancer showing normal (arrow)and malignant nodes (circle). Notice the size of nodes is less than 5mm.

Table 1. Comparison of Combidex ® and Feraheme®

	Combidex® (Ferumoxtran-10)	Feraheme® (Ferumoxytol)
Particle size	<50 nm	17-31 nm
Amount of iron per vial	210 mg	510 mg
Volume per vial	10.5ml	17ml
Amount of iron/ml	20mg/ml	30 mg/ml
Injection rate	4ml/min with 100 cc N/S	1 ml/sec (30 mg/sec)
Dose	2.6 mg of Fe/kg	510 mg/dose - can be repeated after 3 days of the first dose

The primary goals of the study are to evaluate 1) if Feraheme-enhanced MRI is capable of producing a diagnostic quality of images (technical feasibility) and 2) if Feraheme-enhanced MRI is capable of identifying malignant node as malignant and benign lymph node as benign, once the MRI is technically optimized (clinical feasibility). This study will be a strong foundation of future investigation of the true value of USPIO-enhanced lymph node imaging in clinical patient care and will open the door to the clinical implementation of a non-invasive lymph node imaging in oncologic patients.

Additional potential benefit of USPIO is dramatic improvement of the vascular enhancement on T1-weighted MR images for a length of time during early vascular phase and the contrast has been suggested to use for MR angiography [20] and dynamic liver imaging [21]. In liver imaging, if the early vascular phase of images can be acquired at the same setting with the MR lymph node imaging (MR-LNI), the additional Gd-enhanced MRI may be eliminated in some patients who require reticular endothelial system of liver or lymph node imaging.

In this study, we will also explore the capability of Feraheme-enhanced MRI in producing a diagnostic quality of early vascular phase imaging of liver (technical feasibility).

2.0 Objectives

Primary Objectives:

1. To evaluate if the Feraheme®-enhanced MR-LNI is capable of producing diagnostic quality of images once the imaging parameters, including the scan time, are optimized.
2. To evaluate the clinical feasibility of MR-LNI in oncologic patients

Exploratory Objectives:

Explore the technical feasibility of Feraheme® use in an early vascular phase of liver imaging

3.0 Patient Eligibility

Patient Selection

A total of 18 patients (maximum allowable sample size with an available fund) will be enrolled.

Inclusion Criteria

1) Enrolled at MDACC, Written consent
2) Measurable nodes on the recent cross sectional imaging (CT, MRI. US) or suspicous lymph nodes for metastasis
3) Requiring tissue diagnosis (FNA, core biopsy, surgical biopsy, surgical resection), or clinical follow-ups for at least 6 months.
4) Any and all primary disease sites in the abdomen and pelvis will be allowed

Exclusion Criteria

1. Primary or secondary iron overload
2. Lactation or pregnant - women with child bearing potential will be excluded
3. Contraindications for MRI
4. Contraindication or allergy to Feraheme® (based on insert)
5. Clinically documented or risk of primary or secondary iron overloading (e.g. History of thalassemia, sickle cell anemia, hereditary hemochromatosis, multiple transfusions with any reason), anemia not caused by iron deficiency
6. Age under 18

4.0 Study Plan and Methods

1. Technical feasibility of Feraheme®-enhanced MR-LNI

1. A total of 18 patients will be selected in a consecutive fashion. The patients will be referred by one of the clinical collaborators and screened and consented by a research nurse, PI or radiologist collaborators.

2. Based on our previous experience with Combidex® and on-going experience of the investigators at Massachusetts General Hospital (MGH) (unpublished data), we will begin with the similar imaging parameters that were used previously. The imaging parameters will be adjusted as needed to optimize the visualization of the nodes.

[Although this process is unpredictable, it may take about 5-10 patients in initial optimization of the imaging parameters and additional 5-10 patients in identification of an optimum scan time. We expect that there will be an overlap of patients between these 2 processes. When image parameters cannot optimize with the first 10 patients, the study will be terminated.]

3. MRI will be acquired prior to the injection of Feraheme® and repeated at approximately 48 hours and 72 hours from the time of injection (scan time). The scan time will be adjusted, as needed.

4. Based on the on-going experience of MGH (unpublished data), 6mg of iron/kg (maximum 510mg/dose) will be injected at a rate of 1 ml/sec (30 mg/sec) or slower.

5. In those without pathologic correlation, all nodes will be followed clinically for at least 6 months.
6. The clinical decision will not be based on the results of the MRI.

Exploration of USPIO use in liver imaging

1. Patients undergoing Abdominal MR-LNI for this trial will be selected for additional imaging for liver on day 1.

2. On day 1, additional T1WI will be acquired at arterial, portal venous, and delayed venous phases and 5 minutes, 10min and 30min from the time of injection of Feraheme®. This timing will be modified as needed, depending on our experience of the first couple of patients.

3. Quality of aorta enhancement at each time point will be evaluated subjectively as an indicator of adequacy of vascular phase of liver images.

MRI techniques

All MRI data will be acquired using FDA-approved pulse sequences and radiofrequency coils.

1.1 Technical feasibility of Feraheme® -enhanced MR-LNI

Four pulse sequences will be acquired as part of this trial:

1) A two dimensional (2D) T2-weighted fast spin-echo (T2W-FSE) sequence,
2) a 2D T2*-weighted gradient-echo (T2*W- GRE) sequence,
3) a 2D T1-weighted gradient-echo (T1W-GRE) sequence, and
4) a 3D T1W-GRE sequence.

For each sequence, the section thickness will not exceed 5-mm. The total exam time will not exceed 30 minutes.

The pulse sequence will be modified as needed.

1.2 Exploration of USPIO use in liver imaging
GRE T1WI will be acquired at arterial, portal venous, and delayed venous phases, following a routine dynamic technique, and 5 minutes, 10min and 30min from the time of injection following injection of Feraheme. Conventional dynamic technique will be used for imaging parameters.

The scan time will be adjusted as needed.

5.0 Data Collection and Analysis

All subjective evaluation will be performed based on a consensus of three radiologists.

Optimization of the imaging parameters

1. Based on our previous experience with Combidex® and on-going experience of Massachusetts General Hospital (MGH) (unpublished data), the image data will be collected at approximately 48 hours and 72 hours after the injection of Feraheme®. The scan time will be adjusted as needed.

2. The image quality will be graded subjectively (poor, fair, good).

3. The signal intensity (SI) change of a lymph node between the pre- and post- contrast images will be observed subjectively at each time point. The degree of SI change at each time point, then, will be compared each other subjectively and a time point showing the nodes best (greatest signal loss relative to that on pre-contrast images) will be identified (optimum scan time).

4. In those who undergo biopsy or surgical exploration, pathological status of each evaluated lymph node will be recorded whether they are malignant or benign. In those who do not undergo for the tissue diagnosis, nodes will be followed with routine clinical images (CT or MRI) for at least 6 months. The purpose of this step is to exam the technically optimized Feraheme-enhanced MRI sees the malignant node as malignant and benign nodes as benign by subjective evaluation. A statistical analysis is not applicable at this time.

Exploration of SPIO-enhanced liver imaging
When images of abdomen are available:

1. The overall image quality will be graded subjectively (poor, fair, good).

2. The quality of aorta enhancement will be graded subjectively (poor, fair, good).

3. Statistical analysis is not applicable at this time.

6.0 Adverse Events

Drug Information
Drug Information: Package insert [15]

Adverse Events
Feraheme® may cause serious hypersensitivity reaction and hypotention. The adverse reactions were reported in ≥1% of Feraheme® treated patients for iron deficiency anemia based on the randomized clinical trials. Diarrhea 4.0%, constipation 2.1% and hypotension 1% are among the most common events [15].

Managing and Reporting Adverse Events and Allergic Reaction
In the event of allergic type reaction, the patients will be treated in the same manner of allergic reaction occurred by an iodinated contrast following M. D. Anderson Cancer Center standard practice. The drug toxicity will be evaluated according to M. D. Anderson Guidelines (CTC version 4). Reporting of adverse events will be according to M. D. Anderson Guidelines for AE Reporting.

7.0 References

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