Efficacy of Feraheme as a Lymphatic Contrast Agent in Prostate Cancer

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Background

- There are roughly 200,000 newly diagnosed cases of prostate carcinoma in the United States each year, with 35,000 deaths per year. Due to the marked variability and aggressiveness of this cancer, evaluation for both osseous and lymphatic metastatic disease is important to determine prognostic implications.
Background

- In 2003 Harisinghani et al. (1) demonstrated the efficacy of Combidex in differentiating benign from malignant lymph nodes in patients with prostate carcinoma. The Oncology Drugs Advisory Committee of the United States Food and Drug Administration (FDA) recommended not to approve Combidex for the proposed indication of a lymphatic contrast agent in 2004. Combidex production was halted.

Background

- The same manufacturer of Combidex (AMAG Pharmaceuticals, Cambridge, Mass.) subsequently received FDA approval for Feraheme (Ferumoxytol) for the stated indication of treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD).

- Feraheme is also a superparamagnetic iron oxide nanoparticle coated with a low molecular weight semisynthetic carbohydrate. Feraheme can be administered intravenously, but is a lymphotrophic agent absorbed by macrophages in lymph nodes and in the reticuloendothelial system.
Feraheme

- Ultrasmall superparamagnetic iron oxide (USPIO) nanoparticle coated with a low molecular weight semi-synthetic carbohydrate.
- Administered intravenously, but a lymphotrophic agent absorbed by macrophages in the lymph nodes and reticuloendothelial system.
- Similar in uptake mechanism to Combidex.
Hypothesis

USPIO (Feraheme)-enhanced MRI will be able to detect lymph node metastases with high sensitivity, specificity and accuracy.
Implications

- Early diagnosis of lymphatic metastatic disease
- Improved therapeutic options
- Paradigm shift
  - Conversion of treatment failures to cure/long-term survival
  - Oligometastatic disease treatment geared towards cure
Normal Lymph Node Suppression with MRI

Fig. 1 demonstrates heterogeneous enhancement of bilateral femoral lymph nodes.

Fig. 2 demonstrates a T2* sequence after Feraheme administration. There is complete and homogeneous suppression of signal corresponding to normal uptake of Feraheme by the lymph nodes.
Correlative CT/MR Imaging Suppressed Signal of Normal Lymph Nodes

Fig. 1 demonstrates a left axillary lymph node.

Fig. 2 post contrast T1 weighted image demonstrates enhancement of the left axillary lymph node.

Fig. 3 demonstrates complete and homogeneous suppression of the lymph node on T2* sequencing after Feraheme administration. This corresponds to normal uptake of the Feraheme by the lymph node.
Methods and Materials

152 patients with biochemical recurrence of prostate carcinoma (rising PSA) after definitive treatment underwent IV infusion of Feraheme at 6mg/kg.

3 minor complications were encountered. All patients underwent MR imaging with T2* and T2 MEDIC sequencing 24 hours after infusion. Images were independently reviewed by two board certified diagnostic radiologists. Consensus interpretation was rendered.
Methods and Materials

- 36 patients underwent image-guided lymph node biopsy of the abnormal lymph nodes.
- 2 patients underwent mediastinoscopy.
- 1 patient underwent pelvic lymph node exoneration.
- Radiology-pathology correlation was performed.
Clinical Parameters/Patient Population

All patients status post definitive treatment.
- Radical Prostatectomy
- Brachytherapy
- External Beam radiation

- Mean age 69 yrs.
- Range 42-85 yrs.
Clinical Parameters/Patient Population

- All patients presented with rising PSA s/p definitive therapy.
- All patients receiving medical oncologic management.
  - Hormonal castration
  - Leukine
  - Casodex
  - Ketoconazole
  - Vitamins/ Supplements
Imaging Work Up

- 64 slice helical CT scan (with dynamic contrast enhancement).
- 3T MR Imaging with T2* and T2 MEDIC sequencing followed by fat saturated post Gadolinium T1 weighted sequences.
Imaging Protocol Rationale

3T over 1.5T MR Imaging
- Rapid
- High Resolution
- Large field of view capability
- Reproducible and homogeneous T2* and T2 MEDIC sequencing.
Results

- 27 of the patients demonstrated failure of suppression of pelvic lymph nodes on MEDIC and T2* MR imaging.
- 7 patients demonstrated failure of suppression of retroperitoneal lymph nodes.
- 2 patients demonstrated failure of suppression of mediastinal lymph nodes.
- 3 patients demonstrated failure of suppression of bilateral axillary and supraclavicular lymph nodes.
Results

- 84 lymph nodes demonstrating abnormal T2* signal were sampled.
- 76 lymph nodes demonstrated metastatic prostate carcinoma.
- 2 lymph nodes demonstrated lymphoma.
- 6 lymph nodes were normal.
Results

Malignant Lymph node size
- 7 measured less than 5 mm.
- 32 measured between 5-10 mm.
- 45 measured above 10 mm.
- 47% did not fulfill traditional imaging criteria for malignancy.
Multi Modality Evaluation of Lymph Nodes with image guided radiology – pathology correlation

The following eight slides demonstrate the abnormal lymph nodes defined by Feraheme-enhanced MR imaging, with correlative image-guided tissue acquisition.
Case 1

Fig. 1 demonstrates multiple left axillary and chest wall lymph nodes.

Fig. 2 demonstrates fat saturated T1 weighted enhancing lymph nodes along the left chest wall and axilla (arrows).

Fig. 3 demonstrates hyperintense T2* signal to these lymph nodes after Feraheme administration, considered suspicious for metastatic disease. The patient underwent percutaneous ultrasound guided lymph node biopsy.

Histopathology: metastatic prostate carcinoma
Case 2

Fig. 1 demonstrates an abnormal subcarinal lymph node on contrast enhanced CT examination.

Fig. 2 demonstrates heterogeneous enhancement to the subcarinal lymph node.

Fig. 3 evidences abnormal hyperintense T2* signal after Feraheme administration. The patient underwent mediastinoscopy with biopsy.

Surgical pathology: metastatic prostate carcinoma
Case 3

Fig. 1 demonstrates a homogeneously enhancing left external iliac lymph node.

Fig. 2 demonstrates a T2* sequence post Feraheme lymph node with abnormal hyperintense signal.

Fig. 3 demonstrates CT guided biopsy of the lymph node.

Histopathology: metastatic prostate carcinoma
Case 4

Fig. 1 demonstrates heterogeneous enhancement to a right obturator lymph node on post contrast fat saturated T1 weighted sequencing.

Fig. 2 demonstrates abnormal hyperintense MEDIC signal after Feraheme administration. Notice the bilateral femoral lymph nodes visualized on the fat saturated T1 image which demonstrate normal and appropriate homogeneous suppression of signal after Feraheme administration, consistent with benign lymph nodes (curved arrows).

Fig. 3 demonstrates CT guided percutaneous biopsy of the right obturator node.

Histopathology: metastatic prostate carcinoma
Case 5

Fig. 1 demonstrates a post contrast fat saturated T1 weighted sequence with a homogeneously enhancing abnormal left femoral lymph node.

Fig. 2 demonstrates abnormal hyperintense T2* signal after Feraheme administration.

Fig. 3 demonstrates percutaneous ultrasound guided biopsy of the abnormal lymph node.

Histopathology: metastatic prostate carcinoma
Case 6

Fig. 1 demonstrates a post contrast fat saturated T1 weighted sequence enhancing left obturator lymph node.

Fig. 2 demonstrates abnormal hyperintense T2*/MEDIC signal after Feraheme administration.

Fig. 3 demonstrates CT guided percutaneous core lymph node biopsy.

Histopathology: metastatic prostate carcinoma
Case 7

Fig. 1 demonstrates an enhancing fat saturated T1 post contrast mass at the prostatectomy site.

Fig. 2 demonstrates abnormal hyperintense T2* signal after Feraheme administration.

Fig. 3 demonstrates CT guided biopsy of the abnormal perirectal lymphatic tissue.

Histopathology: metastatic prostate carcinoma
Case 8

Fig. 1 TI post contrast nonfat saturated sequence demonstrates homogeneous enhancement of left para-aortic retroperitoneal lymph nodes.

Fig. 2 demonstrates abnormal hyperintense T2* signal involving the lymph nodes.

Fig. 3 demonstrates percutaneous CT guided core retroperitoneal lymph node biopsy, with 20 gauge core biopsy specimens obtained.

Histopathology: malignant non-Hodgkin’s lymphoma
Multi Modality Evaluation of Lymph Nodes with image guided radiology – pathology correlation

The following slides demonstrate abnormal femoral lymph nodes defined by Feraheme-enhanced MR imaging, with correlative image-guided tissue acquisition.
False Positive

Fig. 1 demonstrates enhancing right femoral lymph nodes.

Fig. 2 demonstrates abnormal hyperintense T2* signal peripherally with central low signal.

Fig. 3 Ultrasound guided biopsy of the right femoral lymph nodes performed same day as MRI.

Surgical pathology: Mature benign lymphocytes
Correlation of Feraheme with Diffusion Weighted Imaging (DWI)

The following slides demonstrate the concordance between Feraheme MR and DWI.
Pelvic Diffusion

Fig. 1  Axial free-breathing diffusion (b800) demonstrates restricted signal involving left obturator lymph node.

Fig. 2 demonstrates abnormal hyperintense T2* signal involving the same lymph node post–Feraheme infusion.
Fig. 1  Axial inverted free-breathing diffusion (b800) demonstrates restricted signal involving left obturator lymph node.

Fig. 2  Coronal Inverted MPR again demonstrates the abnormal lymph node.
Conclusion

With MEDIC/T2* sequences, lack of suppression of signal in lymph nodes after the infusion of Ferumoxytol (Feraheme) highly suggests evidence of lymphatic dissemination of metastatic disease in prostate cancer patients. The findings also suggest a lower limit to the resolution of focal lymph node metastases of 3-4mm. Further correlative studies are needed.
Discussion

It is hoped that the adaptability of this protocol will foster more widespread use of this agent in an attempt to further delineate its ability to define lymphatic metastatic disease. The imaging protocols utilized on these patients are available throughout the United States. It is hoped that the ability to localize micrometastatic lymphatic disease for appropriate radiotherapeutic intervention will yield longer survival in these patients.
Clinical Relevance

- 3T MRI after Feraheme administration has the potential to identify neoplastic nodes down to a resolution of 3-4mm, thereby markedly improving the detection of metastatic lymph node disease in prostate cancer patients, and helping to guide further therapy.