Gadobenate dimeglumine (MultiHance®) in Magnetic Resonance Mammography (MRM)

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Introduction

Breast cancer is the most common cancer in women in the United States1 and is second only to lung cancer in terms of cancer deaths in women. Optimum treatment requires early diagnosis of the primary tumor before it metastasizes outside the breast. Preliminary investigations indicate that MRI may have a role to play in the detection and diagnosis of breast cancer. MRI enhanced with gadolinium has been shown to be a sensitive technique for the detection of breast cancers2.

MultiHance (Bracco SpA, Milan, Italy) is a novel gadolinium chelate currently approved in Europe for MR imaging of the central nervous system and liver which is undergoing development for breast MRI. MultiHance possesses a capacity for weak and transient interaction with serum albumin which results in an approximate two-fold increase in the T1 relaxation rate compared to gadopentetate dimeglumine (Magnevist) at the same concentration3. The albumin-mediated relaxation enhancement may result in advantages for MultiHance over Magnevist and other approved gadolinium chelates in breast imaging, allowing a higher degree of enhancement at the same dose. The present communication describes a Phase II, double-blind, multicenter, randomized, parallel-group trial aimed at evaluating the safety and efficacy of three doses of MultiHance compared to 0.1 mmol/kg Magnevist for MR Mammography.

Methods

189 patients with known or suspected breast cancer received by bolus i.v. injection either 0.05 (n=48), 0.1 (n=47) or 0.2 (n=47) mmol/kg MultiHance or 0.1 mmol/kg Magnevist (n=47). Coronal 3D-GRE-T1w images were acquired pre-contrast and at 0, 2, 4, 6 and 8 min post-contrast. Separate assessment of randomized unenhanced and contrast-enhanced images and combined assessment of unenhanced, enhanced and subtracted images was performed by two off-site blinded readers. Images were evaluated for lesion presence (detection score 0=uncertain, 1=possibly/probably present, 2=definitely present), location, size, morphology, pattern of enhancement, conspicuity and type (malignant/benign). Lesion time-signal intensity curves were generated and lesion matching with on-site final diagnosis (mammography+ultrasound+histology, if available) was performed. Lesion matching with gold standard (on-site final diagnosis) was performed by a third off-site blinded reader.

Efficacy was assessed in terms of the change in Global Lesion Detection Score (average per patient of detection scores of lesions present in the final diagnosis) from unenhanced to enhanced and to combined images. Lesions reported at final diagnosis but missed at MRI were scored as -1. Diagnostic accuracy was analyzed per lesion and per breast for both detection and characterization (malignant/not malignant). Characterization was evaluated only in patients with cytology or histology results available. Safety was assessed in terms of adverse events monitoring, laboratory investigations, vital signs, physical examination pre-dose and 24h post-dose.

Results

The increase from predose to postdose original image set was significant for all dose groups including the Magnevist group (reader 1 $p=0.009$, reader 2 $p=0.01$). For MultiHance, a significant increasing trend with dose was noted by both readers for both the original image set (reader 1 $p<0.001$, reader 2 $p=0.003$) and the combined image set (reader 1 $p=0.003$, reader 2 $p=0.035$). The highest sensitivity values for lesion detection per lesion were observed by both readers in the 0.1 mmol/kg MultiHance group for both the postdose original and combined image sets. Sensitivity for lesion detection was 89.1% and 74.5% (Readers 1 and 2, respectively) for the 0.1 mmol/kg MultiHance combined image sets. The sensitivity values for the Magnevist group were comparable to those of the 0.05 mmol/kg MultiHance group. Sensitivity for lesion detection per breast was comparable for the two highest MultiHance doses (85.1-90.4%), whereas specificity was highest at 0.1 mmol/kg. Consistently lower detection scores and lower sensitivity values were found for 0.1 mmol/kg Magnevist compared to 0.1 mmol/kg MultiHance. As regards diagnostic accuracy for lesion characterization, sensitivities of 69.2% and 85.7% (Readers 1 and 2, respectively) were obtained per lesion for the MultiHance 0.1 mmol/kg group compared to 45.3% and 66% for the Magnevist group. For the combined image sets, comparable sensitivity values were obtained (between 82.9% and 89.7%). Similar results were obtained on a per breast basis. No safety concerns were apparent.

Discussion

A MultiHance dose of 0.1 mmol/kg is safe and effective for breast lesion detection and characterization. Contrast-enhanced MR mammography with 0.1 mmol/kg MultiHance appears to be more sensitive and specific than contrast-enhanced MR mammography with an equivalent dose of Magnevist. This improved performance is most likely due to an increased T1 relaxivity in blood deriving from a capacity for weak and transient interaction with serum albumin (3, 4).

References

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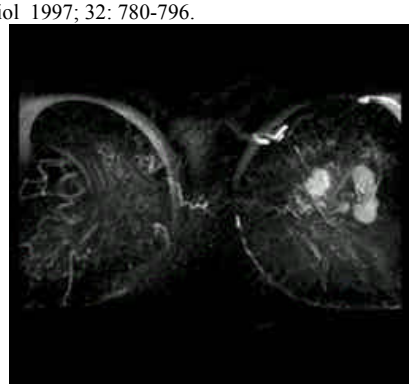
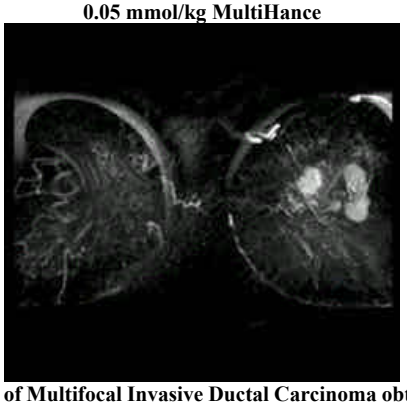


MIP image of Multifocal Invasive Ductal Carcinoma obtained with 0.05 mmol/kg MultiHance



MIP image of Multifocal Invasive Ductal Carcinoma obtained with 0.05 mmol/kg MultiHance