Phase III Double-Blind, Efficacy Evaluation of Gadobenate Dimeglumine (MultiHance™) in Malignant Lesions of the Brain

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RATIONALE

410 patients highly suspected of having lesions of the CNS were studied in two identical phase III clinical trials comparing the safety and efficacy of gadobenate dimeglumine (Gd BOPTA) and gadodiamide (Gd DTPA-BMA). The trials were multicenter in nature and double-blinded. Two incremental dose regimens employing Gd BOPTA were compared to a single such regimen employing Gd DTPA-BMA. The current study focuses on the 81 patients in these two trials with a diagnosis of primary malignant tumor or metastasis of the brain, confirmed by prior CT, MR, or angiography.

METHODS

Patients were randomized to receive one of three incremental dosing regimens of Gd BOPTA or Gd DTPA-BMA. Group 1 received 0.05 mmol/kg Gd BOPTA, followed by a second dose of 0.1 mmol/kg Gd BOPTA at 15 minutes. Group 2 received 0.1 mmol/kg Gd BOPTA, followed by a second dose of 0.1 mmol/kg Gd BOPTA. Group 3 received 0.1 mmol/kg Gd DTPA-BMA, followed by a second dose of 0.2 mmol/kg Gd DTPA-BMA. T2- and T1-weighted scans were obtained prior to contrast injection. The T1-weighted scan was repeated within 5 minutes after the first contrast dose, and then again within 5 minutes after the second contrast dose.

The scans were evaluated by the principal investigator at each site, who was blinded to the cumulative dose and type of agent administered. Pre- and post-dose scans were compared (looking at the first and second dose scans separately) for lesion detection, enhancement, and characterization. A score was assigned for each category from 0 (post-dose images offer no additional information) to 2 (post-dose images offer significant additional information). The three scores were summed for a composite diagnostic information score (range 0 to 6). A 4-point scale with 1=low confidence and 4=high confidence was used for evaluation of the confidence in MR diagnosis.

RESULTS

26 patients were in group 1 (0.15 mmol/kg cumulative dose of Gd BOPTA), 28 in group 2 (0.2 mmol/kg cumulative dose of Gd BOPTA), and 27 in group 3 (0.3 mmol/kg cumulative dose of Gd DTPA-BMA). There were no significant differences in age, weight, or race distribution between the three groups.

Comparing pre and post first dose scans, the diagnostic information composite score was 4.2 ± 1.8 for Gd BOPTA 0.15 mmol/kg, 3.8 ± 2.0 for Gd BOPTA 0.2 mmol/kg and 4.1 ± 2.1 for Gd DTPA-BMA 0.3 mmol/kg. Comparing pre and post second dose scans, the diagnostic information composite score was 4.8 ± 1.6 for Gd BOPTA 0.15 mmol/kg, 4.2 ± 2.0 for Gd BOPTA 0.2 mmol/kg and 4.6 ± 1.8 for Gd DTPA-BMA 0.3 mmol/kg. The second dose resulted in a statistically significant improvement in the diagnostic information composite score for all three dosing regimens (with p values of 0.03-0.04). The increase in diagnostic confidence came from improvements in all three factors: lesion detection, enhancement, and characterization.

The diagnostic information obtained on paired (pre and post dose) first dose scans was equal to that on paired second dose scans in 50% of the patients in group 1, 57% of the patients in group 2, and 41% of the patients in group 3. The diagnostic information on paired second dose scans was greater in 46% of the patients in group 1, 43% of the patients in group 2, and 59% of the patients in group 3. Loss of lesion conspicuity on post-dose scans was seen in only one case in the entire trial, which occurred with Gd DTPA-BMA on both the post first and post second doses. There was a statistically significant difference for all 3 groups (all with $p \leq 0.001$) when the percent of patients whose paired post first dose images offered more diagnostic information was compared to that whose paired post second dose images offered more diagnostic information.

Confidence in MR diagnosis increased from 2.5 predose to 3.5 post first dose to 3.7 post second dose in the 0.15 mmol/kg Gd BOPTA patient group. Similar increases were seen from 2.1 to 3.4 to 3.7 in the 0.2 mmol/kg Gd BOPTA patient group and from 2.4 to 3.1 to 3.6 in the Gd DTPA-BMA patient group.

The percent of patients in whom patient management was potentially affected by contrast administration was 92% and 96% (post first dose and post second dose, 0.15 mmol/kg Gd BOPTA), 89% and 86% (0.2 mmol/kg Gd BOPTA), and 82% and 82% (0.3 mmol/kg Gd DTPA-BMA). The potential change was most commonly in surgical approach, followed by previous treatment modification and choice of initial non-surgical treatment.

CONCLUSIONS

Results with both dosing regimens of Gd BOPTA were similar to that with Gd DTPA-BMA. Cumulative doses of 0.15 and 0.2 mmol/kg of Gd BOPTA provided improvements in diagnostic information similar to a dose of 0.3 mmol/kg of Gd DTPA-BMA. The weak protein binding of Gd BOPTA, with resultant increase in relaxivity, may account for the relative equivalency at lower dose. Efficacy is high with Gd BOPTA use in patients with primary malignant brain tumors or metastases. As with other gadolinium chelates, there is also an incremental improvement with higher dose.