Early DCE-MRI Findings Predict Tumor Volume Changes

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Introduction: DCE-MRI has been used extensively in early phase clinical trials of anti-vascular and anti-angiogenic agents in order to demonstrate biological activity and mechanism of action [1 – 3]. However, to date no large studies have demonstrated a significant link between early changes detected using DCE-MRI and later manifesting clinically relevant endpoints such as reduction in tumor size measured using structural CT or MRI. The primary reasons for this have been a lack of large multi-site clinical studies using DCE-MRI, and a wide diversity of image acquisition and analysis protocols in smaller studies that makes it difficult to pool data across multiple trials. Our group is currently providing image acquisition and analysis support to greater than 30 Phase I and II clinical trials making use of DCE-MRI. All data from these trials have been analyzed using a single standardized analysis software package and standardized procedures. The majority of these trials also make use of a single standardized image acquisition protocol, and roughly half include a structural CT or MRI component. We were able to obtain consent from sponsors of 13 of these clinical trials comprising a total of 164 subjects to include data from their studies in a pooled analysis with the intent of determining the predictive value of early DCE-MRI measurements with respect to changes in tumor burden 8 weeks after the initiation of treatment.

Methods: The number of clinical sites involved in the studies included in this analysis ranged from 1 to greater than 20, and the number of analyzable subjects included from individual studies ranged from 1 to 41. 9 of 13 studies, comprising a total of 107 subjects, used a single standard DCE-MRI acquisition protocol with minor variations to account for differences in scanner make and model. Patients were scanned in the supine position. DCE-MRI data were obtained before, during and after IV administration of 0.1 mmol/kg gadopentetate dimeglumine injected at 3 ml/sec and followed by a 20 ml saline flush at 3 ml/sec. Data were acquired in the oblique coronal plane using the body transmit/receive coil and a 3D fSPGR sequence with TE/TR/FA = 2/5/30. Spacing between slices ranged from 5mm – 8mm, and slab thickness ranged from 8cm – 10cm. Temporal resolution ranged from 6s – 10s, and total number of phases ranged from 22 – 44. Two of the remaining studies, comprising 31 subjects, used a similar protocol with acquisition in the axial plane. The remaining two studies, comprising 26 subjects, used a similar protocol but made use of a torso PA coil rather than the inherent body coil. These two studies also made use of an 0.2 mmol/kg contrast dose. Technical errors during acquisition severe enough to preclude analysis occurred in either the baseline or follow-up DCE-MRI in 8 of 164 eligible subjects (4.9%). These errors included lack of a suitable target lesion (2), failure or irregularity in contrast injection (4), and use of an incorrect coil (2).

Time from DCE-MRI baseline to first dose of study drug in the studies used in this analysis averaged 4 days, with a maximum of 20 days and a minimum of 1 day. Time from first dose to follow-up DCE-MRI scan varied by study and ranged from 4 hours to 15 days. This variation is reflective of the variety of drugs used in these studies. All were intended to affect the tumor microvasculature, but they included both vascular disruptive agents and anti-angiogenic agents as well as both large and small molecules. Time from first dose to follow-up structural CT or MRI scan was generally 8 weeks.

The primary endpoint from the DCE-MRI component of this analysis was K^{Trans} [4], calculated independently at each voxel within the target lesion and reported as the median of the resulting set. The primary endpoint of the structural CT/MRI component of this analysis was tumor volume, summed over up to 10 target lesions. The methods used for calculating K^{Trans} have been previously published [5], as have the methods used for calculating tumor volume [6]. Two of the studies (31 subjects) included in this analysis included a DCE-MRI scan-rescan component. The coefficient of variability for K^{Trans} estimated from these studies was ~10%, which is similar to previously published results using these acquisition and analysis techniques [7,8]. One of the studies (21 subjects) included in this analysis included a structural MRI scan-rescan component. The coefficient of variability for summed tumor volume estimated from this study was 4.9%. Based on these results, a change in K^{Trans} of greater than 20% or a change in summed tumor volume of greater than 10% was considered measureable in this analysis.

Results: The results of this analysis are summarized in Table 1 below. Subjects were ranked according to the reduction seen in K^{Trans} in intervals of 20% change, and then categorized as either Responding (>10% reduction in total tumor volume – 73/156 subjects), Progressing (>10% increase in total tumor volume – 41/156 subjects), or Stable (all other cases – 42/156 subjects). The large majority of these cases were stable according to the RECIST criteria, primarily because changes in tumor diameter are far less sensitive to either response or progression than changes in tumor volume.

Table 1: Summary of analysis results.

	Volume Reduction >10%	**Stable Volume**	**Volume Increase >10%**
K^{Trans} **Reduction >60%**	16/23 (70%)	4/23 (17%)	3/23 (13%)
K^{Trans} **Reduction 40% - 60%**	27/39 (69%)	4/39 (10%)	8/39 (21%)
K^{Trans} **Reduction 20% - 40%**	14/32 (44%)	6/32 (19%)	12/32 (38%)
No Measurable K^{Trans} **Reduction**	16/62 (26%)	28/62 (45%)	18/62 (29%)

Discussion: These results show a clear relationship between early reductions in K^{Trans} measured using DCE-MRI and later reductions in summed tumor volume measured using structural CT or MRI. This relationship is not pronounced enough to predict outcomes on an individual patient basis, as a substantial fraction of DCE-MRI non-responders show volume reductions, while a smaller fraction of strong DCE-MRI responders show volume increases. However, these results may prove useful in interpreting the results of early phase clinical trials using DCE-MRI to assess subject response to anti-vascular or anti-angiogenic agents. The only anomalous result is the higher proportion of Stable Volume subjects with no measurable K^{Trans} reduction relative to the 20% - 40% reduction group. This is likely a result of the fact that tumors with large volume increases frequently show the development of internal necroses. This produces apparent reductions in K^{Trans} even in the absence of effective treatment. Subjects with large volume increases therefore tended to fall into the 20% - 40% reduction group, while subjects with no change in tumor volume were more likely to fall into the no measurable reduction group. It would be both interesting and useful to explore the possible link between early reduction in K^{Trans} and later differences in more generally recognized parameters such as progression free survival or RECIST response rate. This is unfortunately not possible using these data due to the wide variety of primary tumor types represented in these studies and the resulting wide variety of expected rates of tumor growth in the absence of effective treatment. However, as data become available from larger Phase II studies using DCE-MRI as an exploratory endpoint this is an avenue we hope to explore.

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