Relationship between VEGF receptor expression and DCE-MRI tracer kinetic parameters in advanced ovarian cancer

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Introduction  Vascular endothelial growth factor (VEGF), and its receptors VEGFR-1 and VEGFR-2, are key angiogenic mediators in ovarian cancer that greatly enhance tumor vascularity and are associated with poor prognosis. Consequently, there has been an increase in the development of anti-VEGF therapies and integration of imaging strategies to help elucidate the underlying tumor physiology and assess drug efficacy. Dynamic contrast-enhanced MRI (DCE-MRI) may be used to quantify tumor microvascular characteristics through the application of a tracer kinetic model to estimate parameters such as Ktrans (contrast agent transfer coefficient, a composite of blood flow and capillary permeability) and vp (blood plasma volume). This study explores the relationships between serological expression of soluble (s) VEGFR-1 and VEGFR-2 and ovarian cancer angiogenesis as quantified by DCE-MRI in order to gain an insight into the sensitivity of DCE-MRI to such processes.

Methods  Imaging: The local ethics committee approved the study and 8 patients with histologically or cytologically confirmed ovarian or primary peritoneal carcinoma were recruited into the study. All patients had completed chemotherapy treatment at the time of entering the study and had measurable residual disease. Imaging was performed at 1.5 T using a Philips Intera (Philips Healthcare, Best, The Netherlands) MR scanner at baseline (study entry), 4, 8, 12, 18 and 26 weeks. Patients were withdrawn from the study if disease progression (RECIST criteria) was confirmed. The DCE-MRI protocol used an axial 3-D spoiled gradient echo (FFE/SPGR) sequence with baseline (T1 measured using the variable flip angle method with the following parameters: 2°, 10° and 20° flip angles, TR/TE = 4.0/1.00.92 ms, FOV = 375 x 375 mm, matrix = 128 x 128, slices = 25, thickness = 4 mm. The dynamic image acquisition used the same parameters with a flip angle of 20°, 75 dynamic timepoints and a temporal resolution of 5 s. On the sixth dynamic timepoint, 0.1 mmol/kg of body weight of 0.5 mmol/ml Omniscan (GE Healthcare) was administered through a Spectris power injector (Medrad Inc.) at a rate of 3 ml/s followed by an equal volume of saline flush also at 3 ml/s.

DCE-MRI analysis: Regions of interest (ROI) were defined for the whole tumor volume. Enhancing voxels were identified and the extended Kety model was fitted to each voxel’s time series using an automated arterial input function. 3D maps of Ktrans, vp and vp were generated and summarized using median (Ktrans, vp, vp) and mean (vp, vp) summary statistics for each tumor.

Serological markers: Plasma samples were obtained immediately prior to the DCE-MRI scan. Following preparation procedures, samples were analyzed in duplicate using a validated, multiplex ELISA method (Searchlight multiplex ELISAs, Aushon Biosystems). Angiogenic markers VEGFR-1 and VEGFR-2, were analyzed.

Statistical analysis: All paired DCE-MRI and serological markers were pooled on the basis that there was no therapeutic intervention. Scatter plots of Ktrans, vp, sVEGFR-1 and sVEGFR-2 were generated and a bivariate Spearman’s correlation analysis was used to test for significance (p < 0.05).

Results  Significant correlations between sVEGFR-1 and sVEGFR-2 with both vp and Ktrans were observed (Fig. 1). An inverse relationship was seen between sVEGFR-1 and sVEGFR-2 and vp (p = 0.011 and 0.001 respectively). A positive correlation between the serological markers and Ktrans was observed (p < 0.001 and 0.026 respectively). Ktrans and vp were not co-related (p = 0.225), which suggests (but does not guarantee) that in these tumors Ktrans reflects vessel permeability rather than blood flow.

Figure 1: Scatter plots showing correlations between vp (unitless) and sVEGFR-1 (a) sVEGFR-2 (b) (CC = -0.529 and -0.640 respectively) and between Ktrans (units = min^-1) and sVEGFR-1 (c) and sVEGFR-2 (d) (CC = 0.702 and 0.474 respectively). The black line through the data shows the line of best fit.

Discussion  This study has demonstrated the differing relationships of tracer kinetic model parameters, Ktrans (reflecting blood vessel permeability) and vp (blood plasma volume), to the angiogenic mediators sVEGFR-1 and sVEGFR-2 in this group of tumors. One possible explanation for these observations is that in tumors where the blood supply is reduced, and that therefore have a reduced vp, the resulting hypoxic stress leads to overexpression of VEGF and its receptors. This relationship is clearly seen in Fig. 1a/b for both sVEGFR-1 and sVEGFR-2. In the same manner, the hypoxic stress and associated increase in VEGF production with upregulation of sVEGFR-1 and sVEGFR-2 leads to an increase in vessel permeability, measurable by Ktrans (Fig. 1c/d). These findings suggest that the combination of low vp, high Ktrans and high sVEGFR-1/2 may infer local activation of the hypoxia-VEGF system in ovarian tumors. This study demonstrates that appropriate DCE-MRI modeling allows extraction of information specific to the angiogenic process and that these tumor level findings can be related to circulating biomarkers.