Reduction in blood volume and vascular permeability induced by anti-PDGF-R therapy as detected by DCE-MRI

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Introduction

Prostate cancer metastases are frequently found in the bone and are often resistant to conventional chemotherapy. However, substantial therapeutic response was achieved when the cytotoxic drug Paclitaxel was combined with the platelet-derived growth factor receptor (PDGF-R) tyrosine kinase inhibitor imatinib. The improved response was attributed to the effect on tumor-associated endothelial cells. Treatment resulted in reduced phosphorylation of PDGF-R on endothelial cells, fewer tumor-associated endothelial cells, and increased apoptosis in vascular endothelial cells as well as tumor cells (1-3). However, these findings were made by immunostaining, which cannot inform on vascular functionality and cannot be used routinely *in vivo* to monitor response to therapy. We recently showed that macromolecular dynamic contrast enhanced (DCE)-MRI can be used to monitor progression of a prostate cancer bone metastases model (4). Thus, the purpose of this study was to use DCE-MRI to examine changes in vascular function associated with response to anti-PDGF-R therapy in advanced prostate cancer bone metastases.

Methods

Tumor model: Prostate cancer bone metastasis model was initiated by intratibial injection of PC-3MM2 cells ($1x10^5$ cells/20 µl) in male CD-1 nude mice using a 27-gauge needle (2). Mice were imaged weekly by DCE-MRI. Drug therapy was initiated ~one week after tumor exits the bone (d0).
Contrast materials: Biotin-BSA-GdDTPA was synthesized as previously reported (5). An intravenous dose of 10 mg/mouse was used.
MRI experiments: MR images were acquired on a 4.7T Biospec (Bruker Biospin, Billerica, MA) using micro-imaging gradients and a purpose-built knee coil. T2-fSE: TR 4500 ms, TE 15.6 ms, 2 averages, matrix 256x192, FOV 30x30 mm, slice thickness 1 mm. 3D-fSPGR: precontrast flip angles 10, 15, 35, 50, 70 degrees; postcontrast flip angle 35 degrees, TR 10 ms, TE 1.23 ms, 2 averages, matrix 128x128x32, FOV 20x20x20 mm. Vascular parameters, blood volume fraction (fBV) and permeability surface area product (PS), were derived as described (6).
Combined drug therapy (2): Imatinib mesylate, (provided by Novartis Pharma, Basel, Switzerland) was administered at d0, d1 and d2 (50 mg/kg; ip). Paclitaxel (Bristol-Myers Squibb, Princeton, NJ) was administered at day 0 (d0; 8 mg/kg; ip).

Results

MRI studies began two weeks after intratibial injection. Tumor that was replacing the bone marrow was detected as high intensity in the pre-contrast T2W images and as low enhancement relative to normal bone marrow in DCE-MRI (Fig 1a). Over time, the tumor progressed throughout the bone marrow and finally exited the bone (Fig 1b). One week after the tumor was first observed outside the bone (typically at 4-5 weeks; Fig 1c), the intratibial tumor developed fibrotic and necrotic regions characterized by late enhancement and prolonged retention of the macromolecular contrast material (Fig 1c). At the same time, the tumor portion growing outside the bone showed marked early contrast enhancement and accumulation of contrast material (Fig 1d; d0). Short term combined imatinib and paclitaxel treatment resulted in the elimination of this rapid extravasation and accumulation of contrast material (Fig 1e; d2). Parametric analysis indicated a slight decrease in blood volume (fBV) and a dramatic decrease in vascular permeability (PS) following treatment (Fig 1f).

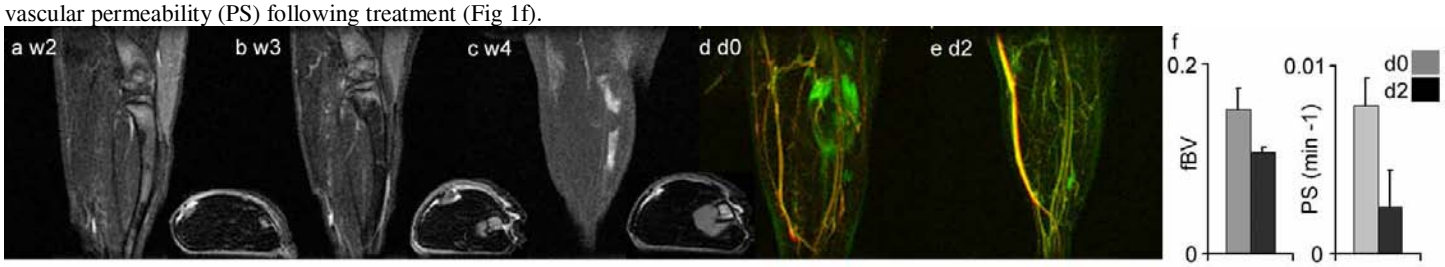

Figure 1. Representative results for one mouse, 2 (a) 3 (b) and 4 (c-e) weeks after tumor inoculation, showing selected coronal slices of 3D-fSPGR, 15 min (a, b) and 48 hr (c) post-contrast, and corresponding pre-contrast axial T2W images (bottom, right). Maximal intensity projections (d, e), are presented as overlay of 1.5 (red) and 45 (green) min post-contrast, at d0 (d) and d2 (e) of imatinib and paclitaxel treatment. Quantitative results (f; n=2): fBV is the ratio between initial tissue concentration of contrast material and blood concentration. PS is the initial contrast accumulation rate normalized to blood concentration. Values are averaged for outer tumor rim.

Discussion

These results provide the first in-vivo demonstration of the anti-vascular effect induced by the combined imatinib and paclitaxel therapy in an advanced-stage prostate cancer bone metastases model. Moreover, the extent of the reduction in vascular function detected by macromolecular DCE-MRI is very dramatic and comparable to that previously observed upon withdrawal of VEGF in a tetracycline regulated system (5). Next we propose to monitor anti-PDGF-R therapy in the early stages of bone infiltration where changes in DCE-MRI are expected to reflect tumor regression or a decrease in interstitial fluid pressure. Our findings also illustrate the value of DCE-MRI in monitoring neovascularization following PDGFR activation as well as response to anti-PDGFR treatment in tumor metastases.

References

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