Dynamic Contrast Enhanced Magnetic Resonance Imaging Evaluates Early Therapeutic Effect of Anti-EMMPRIN Antibody with Cisplatin or X-radiation in Head and Neck Cancer Mouse Models

Hyunki Kim[1], Yolanda Hartman[1], Guihua Zhai[1], Thomas Chung[1], Melissa Korb[1], Tong Zhou[1], and Eben Rosenthal[1]
[1]*University of Alabama at Birmingham, Birmingham, AL, United States*

Purpose: To evaluate the early therapeutic effect of anti-EMMPRIN antibody in combination with conventional cytotoxic therapy including cisplatin or X-radiation in head and neck cancer mouse models using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).

Materials and Methods: A total of 12 groups of female athymic nude mice (4-6 weeks old) bearing subcutaneous SCC1 (groups 1-6) or OSC19 tumors (groups 7-12) were used (n=5/group). Groups 1-6 (or groups 7-12) were untreated (served as control) or treated with anti-EMMPRIN antibody (0.1 mg, days 0 and 3), X-radiation (2Gy, days 0 and 3), cisplatin (3mg/kg, day 0), anti-EMMPRIN antibody plus X-radiation, and anti-EMMPRIN antibody plus cisplatin, respectively. MRI was applied on days 0, 3, and 7 with 9.4T system (Bruker BioSpin Corp., Billerica, MA). Anatomical MRI to measure tumor volume was performed using RARE T2-weighted turbo spin-echo sequence with the following acquisition parameters: TR/TE=2000/34 ms, 128x128 matrix, and a 30x30-mm FOV. Continuous 1-mm thick slices were used to cover the entire tumor region. T1 map was acquired with a gradient-echo multiflip-angle approach with the following parameters: TR/TE=115/3 ms, 128x128 matrix, a 30x30-mm FOV, NEX=4, and seven flip angles of 10, 20, 30, 40, 50, 60, and 70°. A total of five to seven 1-mm thick slices were acquired to cover tumor regions of interest in an interlaced mode. DCE-MRI employed the same acquisition parameters as those above but with the fixed flip angle of 30°. Five baseline images were acquired before gadoteridol injection, and then 40 images were acquired after gadoteridol injection of 0.0267 mmol/ml over a period of 15 seconds with a total injection volume of 0.15 ml. The reference region (RR) model was employed to calculate K^{trans} values. All tumors were collected on day 7, and Ki67 and CD31 staining were implemented. Ki67 expressing cell density (cell number/mm^2) and CD31 density (CD31-stained area/total area) were calculated.

Results: Anti-EMMPRIN antibody suppressed the mean tumor growth about 50% for 7 days in both the models (Fig. 1) and reduced both Ki67 and CD31 expressing cell densities significantly ($p<0.05$). However, of interest, the mean K^{trans} value of SCC1 tumors treated with radiation increased about 40% for 3 days after therapy initiation, but in the OSC19 model, radiation significantly reduced tumor K^{trans} values during the same time period ($p<0.0001$). Figure 2 shows the correlation between tumor K^{trans} change for 3 days (ΔK^{trans}_{3D}) and tumor volume change for 7 days (ΔV_{7D}). In OSC19 model, ΔK^{trans}_{3D} was significantly correlated with ΔV_{3D} ($p=0.0054$), ΔV_{7D} ($p=0.0053$), Ki67 expressing cell density ($p=0.0138$), and CD31 density ($p=0.0343$), but, in SCC1 model, ΔK^{trans}_{3D} was not significantly correlated with any of those ($p>0.05$). However, when the group treated with X-radiation was excluded, the significant correlation was found in SCC1 model ($p<0.05$) (Fig. 2B). ΔK^{trans}_{7D} was significantly correlated with ΔV_{7D}, Ki67 expressing cell density, and CD31 density in either SCC1 or OSC19 model, with/without X-radiation treated group ($p<0.05$).

Discussion: K^{trans} increase during early period of radiation in SCC1 tumors might be caused by the differential radiation susceptibility of endothelial cells in tumors. When intratumoral endothelial cells susceptible to X-rays are preferentially killed by radiation, MR contrast can leak out through the empty space on the vessel wall, which results in the rapid increase of wash-in rate (K^{trans}). Thereafter the vessels will be reassembled with X-ray resistant endothelial cells, leading to the reduction in K^{trans} value as well as microvessel density. However, since X-ray susceptibility of endothelial cells can be different across tumor types, it would be difficult to determine the optimal time point of the follow-up DCE-MRI to assess the therapeutic efficacy. Therefore DCE-MRI may be used to predict therapeutic efficacy of anti-EMMPRIN antibody and cisplatin in head and neck cancer, but not with radiation.

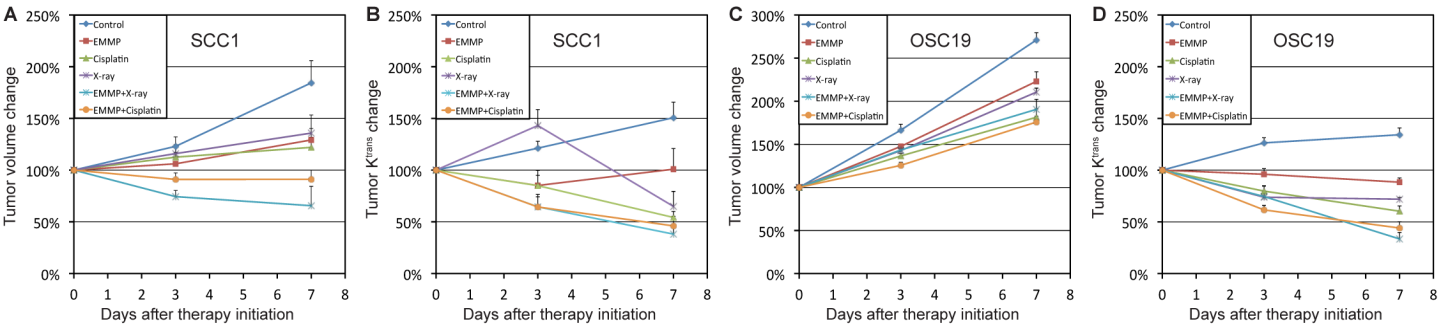

Figure 1. *In vivo* tumor volume and K^{trans} change in HNSCC preclinical models. (A, C) Tumor volume and (B, D) K^{trans} changes of (A, B) SCC1 and (C, D) OSC19 tumors for 7 days after therapy initiation.

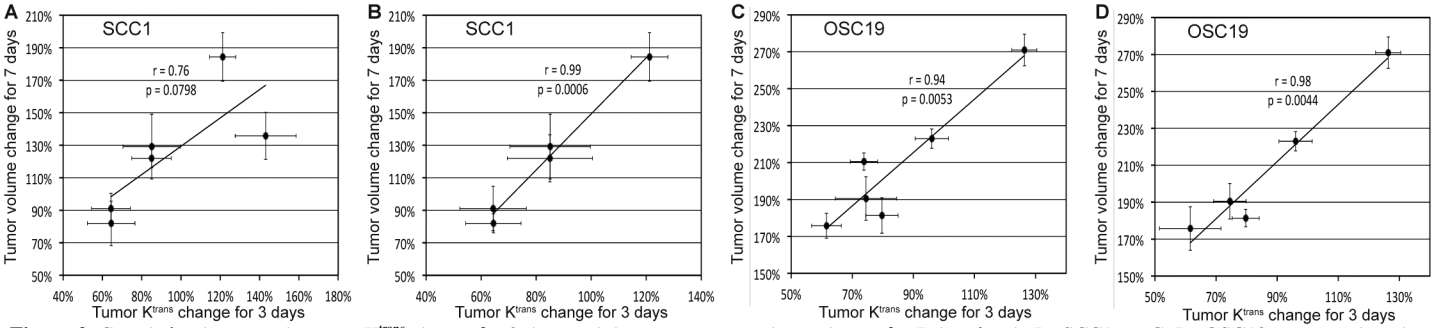

Figure 2. Correlation between the mean K^{trans} change for 3 days and the mean tumor volume change for 7 days in (A, B) SCC1 or (C, D) OSC19 tumors, when data of X-radiation monotherapy were (A, C) included or (B, D) excluded.