Therapeutic effect of bleomycin and doxorubicin on Skin tumors: Assessment by MRI

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OBJECTIVE

To evaluate the potential of MRI determined tumor volume, T1 and T2 parameters in predicting the efficacy of chemotherapeutic agents on Squamous cell carcinoma of skin.

INTRODUCTION

Squamous cell carcinoma (SCC), second commonest form of skin cancers, arises from keratinocytes (1,2). Early assessment of therapeutic response of SCCs save patients from toxicity of ineffective therapy and provides the options of initiation of second line therapy and early surgery. MR imaging has the potential to detect response of chemotherapeutic effect in discretely localized regions of the skin tumor (3, 4) but also provides useful information about correlation with water content or interactions of water proton molecules. However, a complete and fundamental understanding of the effects of tissue organization and structure on T1 and T2 times in biological tissues after chemotherapy is not currently available. Thus in the present study, we monitored and evaluated the synergistic effects of multidrug therapies by visualizing the subpopulation of cells killed by the individual therapeutic modalities using MR derived parameters.

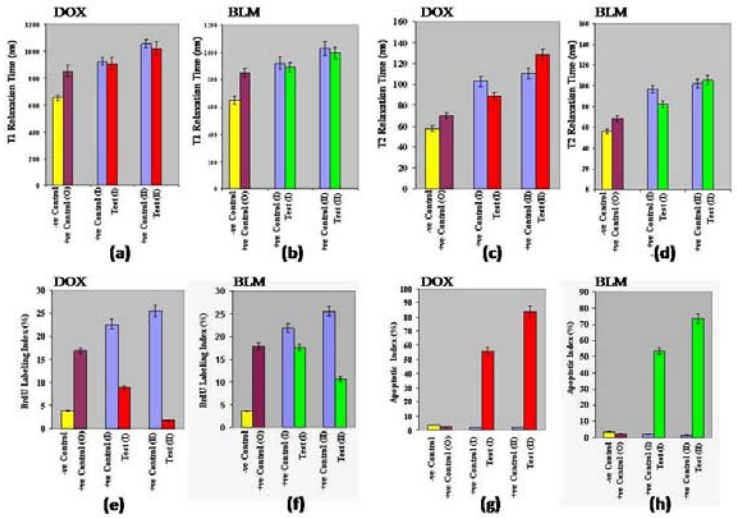
METHODS

Animals were anesthetized before MRI with a combination of thiopentone (40mg/kg) and diazepam (8mg/kg) *i.p*. All imaging experiments were performed on a 4.7 T animal scanner (Bruker BIOSPEC, Germany) using 35-mm diameter volume resonator transmitter/receiver coils and a 40 x 40 mm field of view (FOV) in normal (Normal), tumor (Control) , doxorubicin (DOX) and bleomycin (BLM) treated tumor (Test) groups respectively. The other groups, Control-I, Control-II, are tumor bearing mice with 16 and 18 weeks old tumor respectively while Test-I and Test II are the corresponding groups which were given respectively 2 and 4 weeks doxorubicin and bleomycin therapy. Spin-echo pulse sequence using an acquisition matrix size of 256 x 256 corresponding to the spatial resolution of 235 x 235μM with a 2 mm thickness was used. T1 experiments consisted of running two-dimensional spin-echo imaging sequence at variable recovery times (TR). A plot of ln[1-M(t)/M(0)] vs. TR was made for the calculation of T1. T2 experiments consisted of running a multi-spin multi echo (MSME) sequence with different TE values. T2 was obtained from the plot of ln[1-M(t)/M(0)] vs. TR. Tumor proliferation by BrdU assay and apoptotic index by TUNEL assay were done as explained earlier (2) .It must be mentioned here that the MRI, proliferation assays and TUNEL assay experimental data correspond to the same animal. The Institute animal ethics committee approved the study. Statistical analyses were carried out using statistical software SPSS 11.5.

RESULTS

Figure 1 shows the effect of anti cancer drugs (DOX and BLM) on skin tumors; the relaxation times, T1 (a, b) and T2 (c, d) in the upper panel and the proliferation index (e, f) and apoptotic index (g, h) in the lower panel. There is no significant difference in T1 of tumors after treatment with both DOX (p>0.01) (Figure-1,a) as well as BLM (p>0.02) (Figure-1,b) Test groups with respect to control group.

Figure-1



DISCUSSION

MRI parameters were correlated with histological findings in the progression and regression of skin tumors of SCC. Analysis showed that after 4 weeks of DOX treatment, T2 was longer (128±3msec) in Test-II than Test–I group (111±2msec) (Figure-1,c). There is no significant difference in T1 of tumors after treatment with both DOX (p>0.01) (Figure-1,a) as well as BLM (p>0.02) (Figure-1,b) with respect to control groups. On other hand, T2 decreased (82±4) in Test-I with respect to control-I at 2 weeks while it increased (105±2) in Test-II group with respect to their control group at 4 weeks of BLM treatment (Figure-1,d). Reduction of tumor volume by 79% after DOX treatment and by 31% after BLM was confirmed by a drastic fall in the proliferation index (Figure-1,e &f). The results reveal greater decrease in tumor volume and proliferation index, longer T2 and higher apoptotic index with DOX treatment as compared to BLM, which strongly suggests a higher efficacy of DOX than BLM in skin cancer. Results indicate that MRI can be efficient clinical tool in the prediction of response of tumor to various therapeutic agents.

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