Adaptive Therapy: A Novel Cancer Treatment Regimen Using MRI.

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Introduction: Disseminated cancers are typically treated with the highest possible dose of drug (i.e. maximum tolerated dose to achieve with the explicit goal of killing as many tumor cells as possible). However, these therapies usually fail as the tumors develop resistance in part due to high cellular heterogeneity with multiple microenvironments that can coexist within a same tumor. It has been demonstrated, using mathematical models of Darwinian dynamics, that a treatment therapy that adapts its dose to the tumor spatial variability and tumor microenvironment, promotes the growth of tumor chemosensitive cells at the expenses of the chemoresistant ones (Figure 1). In this treatment strategy, chemotherapy doses are designed to keep the sensitive cells in check. In turn, the sensitive cells, in the absence of therapy, will outcompete the resistant cells due to the fitness cost of resistance to this general strategy termed Adaptive Therapy (AT).[1] Herein, we present in-vivo preclinical MRI methods that have been used to *fine tune* the AT treatment algorithm with the focus on clinical translation.

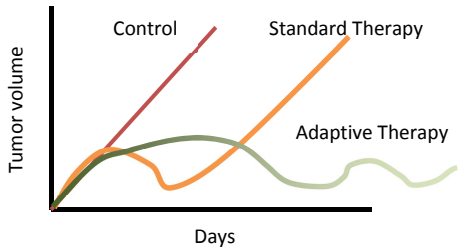

Figure1. Schematic representation of different tumors growth depending on the treatment therapy

Methods: Three cohorts (composed of 10, 12, and 14 mice) of nude mice were injected with 10 million of MDA-MB-231 (triple negative breast cancer) cells in the mammary fat pad. Control animals received sham injections. One group received standard therapy (20mg/kg twice per week for a total of 5 times. The last group received AT, with the Paclitaxel dose modified according to the AT treatment algorithm (Table 1). The treatment period was limited to 100 days. Initially the tumor growth was monitored using caliper measurements. When the tumors achieved a volume of, approximately, 300 mm^3, MRI experiments (T_2 and ADC weighted experiments) were performed on a horizontal Agilent ASR 310 7 Tesla scanner, with 205/120/HDS gradients and 310 mm bore. Axial T_2-weighted fast spin-echo multislice (FSEM) sequences were acquired using an echo time (TE) of 72 ms, repetition time (TR) of 1000 ms, field of view of 35 x 35 mm, matrix set at 128 x 128 and slice thickness of 1.5 mm. Spatial resolution for these scans was thus kept at 273 µm. Applying an identical slice plane, a diffusion weighted sequence using three b-values (50, 500, 1000) and TE/TR = 36/1325 ms was also acquired. Image reconstruction and volumetric analysis were performed in VnmrJ (Agilent Technologies Inc.). Images were processed with an in-house developed MATLAB script to obtain reliable information from these images, as is the viable cell volume.

Table 1: Adaptive Therapy treatment algorithms

Batch #1	Initial Dose = 15 mg/kg > If $V_T^{(n)} \geq 1.1*V_T^{(n-1)}$ →Dose increased by 20% > If $V_T^{(n)} \leq 0.9*V_T^{(n-1)}$ →Dose decreased by 20% Lower Limit: 100 mm^3 and skip the dose.
Batch #2	Starting dose = 15 mg/kg > If $V_T^{(n)} \geq 1.25*V_T^{(n-2)}$ →Dose = 15 mg/kg > If $V_T^{(n)} \leq 1.25*V_T^{(n-2)}$ →Skip Dose
Batch #3	Initial Dose = 20 mg/kg (highest dose) > If $V_T^{(n)} \leq .8*V_T^{(n-1)}$ →Dose decreased by 50% > If $V_T^{(n)} \geq 1.2*V_T^{(n-1)}$ →Dose increased by 50% > If the tumor volume is within 20% range, we will apply same dose as previous dose. Lower Limit: 150mm^3 and skip the dose

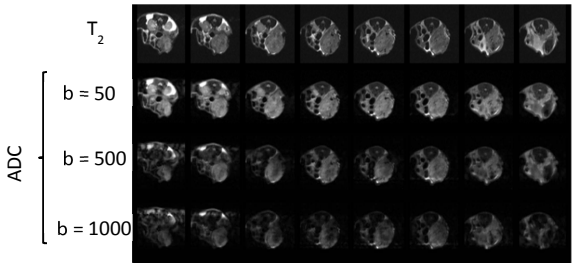

Figure 2. T_2 and ADC weighted images of a tumor corresponding to a mouse with the Standard Therapy.

Results & Discussion: Tumor growth was monitored during the treatment period using the MRI techniques previously described. After the initial encouraging results (batch #1), the AT treatment algorithm has been modified trying to *fine tune* the dose and scheduling. Among these three AT attempts, the last one has shown a positive result. As shown in figure 3, only the AT group (these data contains the Standard Deviation bars because they correspond to 4 animals) has shown a stable small tumor volume. New experiments are currently underway in order to get more information and a deeper insight on how the AT can benefit the in-vivo cancer treatment. In summary, initial results demonstrate that adaptive therapy, guided by MRI measurement of tumor volume, can maintain a stable small tumor burden with prolonged progression free survival compared to standard high dose therapy.

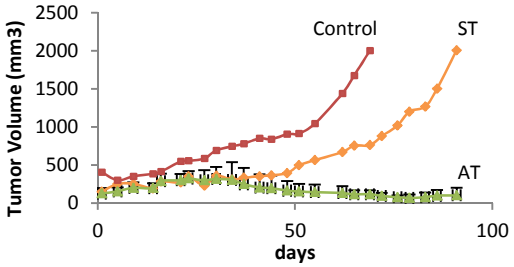

Figure 3. Experimental results showing the MRI tumor volumes of Control, Standard, and Adaptive Therapy groups for the last algorithm.

1. Robert A. Gatenby *et al.* Cancer Res 2009; 69:(11).