

**Evaluation of the radiation enhancer, motexafin gadolinium (MGd), for microbeam radiation therapy of subcutaneous mouse EMT-6**

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Beamline(s): X17B1

**Introduction:** Single-fraction microbeam radiation therapy (MRT) using arrays of parallel thin (<100 μm) slices of synchrotron-generated x-ray beams was shown earlier to have a higher therapeutic index than conventional radiation therapy in controlling mouse subcutaneous EMT-6 tumors [1]. Irradiation was administered in the “co-planar” and the “cross-planar” modes, the latter using two arrays impinging on the target from the same direction, one with vertical and one with horizontal microbeam planes. Here, we report the effect of a radiation enhancer, motexafin gadolinium (MGd, or Xcytrin<sup>®</sup>), on the cross-planar MRT of subcutaneous EMT-6 tumors. MGd is a pentadentate aromatic expanded porphyrin being developed as a sensitizer in radiotherapy and chemotherapy [2]. It selectively biolocalizes in tumor, and can form long-lived radicals in oxic and anoxic conditions [2,3]. Phase II clinical trials with MGd have indicated enhanced tumor regression in radiation therapy of brain metastases [4].

**Methods and Materials:** Fourteen days before irradiation, an EMT-6 cell suspension was prepared in regular culture medium, and 2.5 x 10<sup>5</sup> cells were injected subcutaneously (SC) in the flanks of stock mice for the production of source tumor. Small chunks of source EMT-6 tumors were then transplanted SC into the calf area of the mice’s right hindlegs. The mice were stratified by tumor volume into 5 matched experimental groups with 7-8 mice per group. Two groups of tumor-bearing mice were given 5 daily injections of MGd before irradiation (20 μmolar/kg intraperitoneal (IP) for Day 1, 40 μmolar/kg IP for Days 2-4, and 40 μmolar/kg intravenous (IV) 2-5 hours before irradiation). Single-fraction, cross-planar MRT (90-μm beam width, 300-μm center-to-center beam spacing, 100-keV median beam energy) was used for the irradiations, with an array size 20 mm wide. The in-slice entrance doses were 410 and 650 Gy. Another 2 groups of tumor-bearing mice not injected with MGd were irradiated the same as control groups. The unirradiated tumor-bearing controls also received the same MGd administration as the irradiated ones.

**Results:** All 8 mice in the unirradiated control group had to be euthanized by Day 16 postirradiation. The following table shows the results of tumor ablation and normal tissue response. Comparing our cross-planar microbeams with broad-beam irradiations, it was evident that cross-planar MRT considerably ameliorated normal tissue damage, while ablating a similar or higher percentage of tumors. Comparing the cross-planar results with and without MGd, a slight increase in the number of tumor ablations was observed with MGd at both doses; this increase brought the ablation at 650 Gy to 100%. Noting that this is a single study with limited statistics, we concluded that the combination of MRT and MGd is promising and requires additional investigation. Earlier, using mice with an intramuscular EMT-6 tumor model together with broad beam irradiations, Miller et al. [5], showed that MGd increases the therapeutic efficacy by at least two-fold. The major difference compared with our high-dose irradiation was that they used relatively lower doses of 2.5, 5, and 10 Gy, and a median survival day as the index for calculation and comparison.

Irradiation Method	Radiation Dose (Gy)	Tumor Ablation	Moist Desquamation	Complete Epilation	For Tumor-Surviving mice (i.e., cured)
					Failure of Nearly Full Hair Regrowth in 150 Days
Cross-planar Microbeams (No MGd)	410	4/8	0/8	1/8	1/3
	650	6/7	0/7	2/7	3/6
Cross-planar Microbeams (Plus MGd)	410	5/7	0/7	1/7	1/5
	650	8/8	0/7	4/8	5/8
Broad-Beam (No MGd)	23	1/8	0/8	0/8	0/1
	30	3/8	0/8	2/8	2/3
	38	3/7	0/8	5/8	3/3
	45	6/8	7/8	6/8	4/4

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