Clinical Radiosensitization: Why it does work? From bench side to clinical trials

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ABSTRACT:

Nanoparticles containing high-Z elements are known to boost the efficacy of radiation therapy. Gadolinium (Gd) is particularly attractive because this element is also a positive contrast agent for MRI, which allows for the simultaneous use of imaging to guide the irradiation and to delineate the tumor. Here, we used Silica-based gadolinium nanoparticle (Si-GdNP) -Known as AGuIX®- for brain melanoma metastases. After intravenous injection into animals bearing B16-F10 brain tumor, some Si-GdNP remained inside the tumor cells for more than 24 hours, indicating that a single administration of nanoparticle might be sufficient for several irradiations. Combining AGuIX® with radiation therapy increases tumor cell death *in vitro*, and improves the life spans of animals bearing multiple brain melanoma metastases. These results provide preclinical proof-of-concept for a phase I clinical trial.

I. Introduction

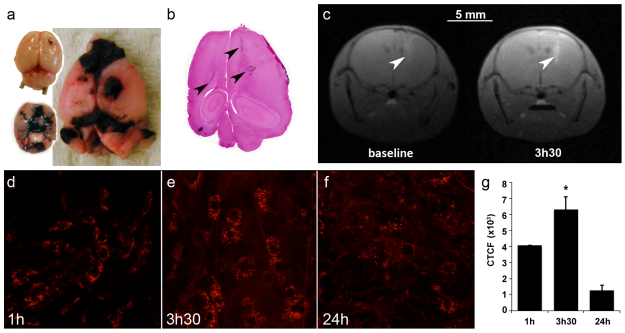
Despite recent outcomes(1), melanoma is still difficult to treat due to multidrug and radio-resistance. In approximately 80% of cases, malignant melanoma tends to metastasize into the central nervous system; this dissemination has a considerable effect on overall patient survival. Radiation therapy is currently prescribed to more than 50 % of brain tumor cancer patients(2). However, effective treatment is often limited by tumor visualization and collateral damage of healthy tissues. One possibility to overcome this problem, besides using a local approach such as stereotactic radiosurgery, is combining radiation with nanoparticles containing high-Z elements, which boost locally the efficacy of radiation exposure during cancer therapy.

II. Material and methods

AGuIX nanoparticles were obtained as previously described(3). *In vivo,* B16F10 mouse melanoma cell was orthotopically grafted into mouse brains to mimic human melanoma brain metastases. After intravenous injection of 10 mg of AGuIX into mice bearing B16F10, MR and intravital two-photon microscopy imaging were performed to determine the maximum tumor uptake, and tumor *vs.* healthy tissue ratio before radiation therapy. Similar to clinical workflow, an image-guided cone-beam CT (CBCT) was performed prior to irradiation exposure to calculate the delivered dose during whole brain radiotherapy (WBRT) to the brain, the metastases and other organs at risk.

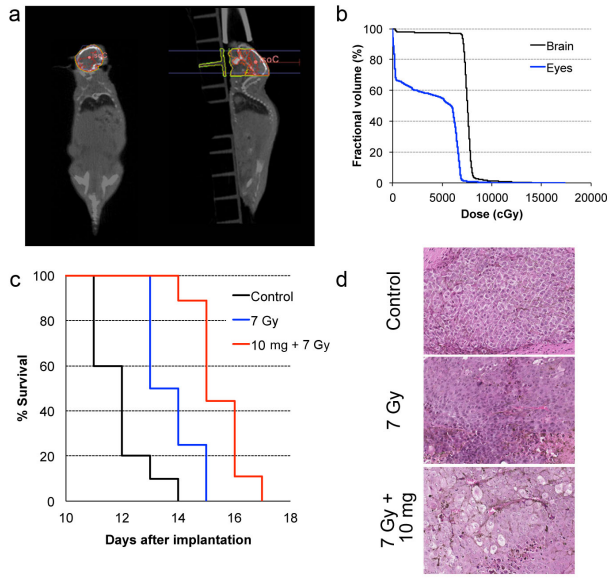
III. Results

III. a-Tumor model and protocol adjustment



Brain tumor distribution of AGuIX®. (a) Mouse brain 5 and 10 days after B16-F10 implantation and (b) the corresponding H&S staining section. The arrows indicate the localization of tumor metastases. Note that metastases are black due to the high secretion of melanin. (c) T1-weighted images of brain of B16F10- bearing mouse. The images were acquired before and 3.5 hours after an intravenous injection of 0.2 ml of particles (50 g/L) at day 5. (d-f) Intravital two-photon microscopy of labeled particles at 1 hour, 3.5 hours and 24 hours after injection, and (g) the corresponding normalized cell fluorescence (CTCF).

III.b Radiation exposure and overall survival



***In vivo* radiation exposure.** (a) Coronal and sagittal views for cone-beam CT performed for the treatment planning. (b) Dose-volume histogram (DVH) showing the percentage of the volume receiving the prescribed dose in the brain region, including the metastases and the eyes (7 Gy in fraction with unique vertical beams). (c) Kaplan-Meier survival curve comparison obtained for brain B16-F10 metastases-bearing mice without treatment (black curve, n=10), those only treated with 7 Gy radiation exposure (blue curve, n=8), and those treated with a combination of nanoparticle (10 mg, 3.5 hours after IV injection) and 7 Gy radiation exposure (red curved, n=9). (d) H&E staining of brains in the different condition.

IV. Discussion and conclusion

The accumulation of AGuIX® in the tumor occurs through the enhanced permeability and retention effect (EPR). The Tumor to healthy tissues of IV injected AGuIX® is favorable for both imaging and therapy for a window of several hours, although the exact kinetics will be patient and tumor specific. Based on the imaging investigations performed on B16F10 bearing mice, the therapeutic irradiation was performed five days after tumor implantation and 3.5 hours after IV injection for highest tumor to healthy tissue ratio. The pathology is very aggressive without any survival for more than 14 days after tumor implantation for the control group. After a single 7-Gy radiation exposure, the increase in life span (ILS) was 8.3 % for the animals that were only irradiated and increased to 25 % with the injection of AGuIX® prior to radiation, corresponding to a 3-fold higher treatment efficacy (p=0.0025) when compared to control group. Clinically, AGuIX® could be useful for several clinical applications. In addition to enhanced radiation therapy, MRI contrast enhancement would be beneficial for treatment planning simulation, patient set-up and real-time guidance. Extensive studies performed in rodents and non-human primates, demonstrated no adverse effects even at high repeated doses. These studies combined supply a strong rationale for future clinical trials.

V. References

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