Experimental set-up for FLASH proton irradiation of small animals using a clinical system

**Summary**

**Purpose**

Recent *in vivo* investigations have shown that short pulses (FLASH) of electrons are less harmful to healthy tissues, but just as efficient as conventional dose-rate radiation to inhibit tumor growth. In view of the potential clinical value of FLASH and the availability of modern proton therapy infrastructures to achieve this goal, we herein describe a series of technological developments required to investigate the biology of FLASH irradiation, using a commercially available clinical proton therapy system.

**Methods and materials**

Numerical simulations and experimental dosimetric characterization of a modified clinical proton beamline, upstream from the isocenter were performed with Monte Carlo toolkit and different detectors. A single scattering system was optimized together with a ridge filter and a high current monitoring system. In addition, a submillimetric set-up protocol based on image-guidance using a digital camera and an animal positioning system was also developed.

**Results**

The dosimetric properties of the resulting beam and monitoring system were characterized: linearity with dose rate and homogeneity for a 12×12 mm² field size were assessed. Dose rates exceeding 40 Gy/s at energies between 138 and 198 MeV were obtained, enabling uniform irradiation for radiobiology investigations on small animals in a modified clinical proton beam line.

**Conclusion**

This approach will enable us to conduct FLASH proton therapy experiments on small animals, specifically for mouse lung irradiation. Dose rates exceeding 40 Gy/s were achieved, which was not possible with the conventional clinical mode of the existing beamline.
Sylvain Thierry, Wael Jdey, Solana Alculumbre, Vassili Soumelis, Patricia Noguiez-Hellin, Marie Dutreix (2017 Sep 27)
The DNA repair inhibitor Dbait is specific for malignant hematologic cells in blood.
Molecular cancer therapeutics: DOI : molcanther.0405.2017

Summary

Hematologic malignancies are rare cancers that develop refractory disease upon patient relapse, resulting in decreased life expectancy and quality of life. DNA repair inhibitors are promising strategy to treat cancer but are limited by their hematologic toxicity in combination with conventional chemotherapies. Dbait are large molecules targeting the signaling of DNA damage and inhibiting all the double-strand DNA break pathways. Dbait have been shown to sensitize resistant solid tumors to radiotherapy and Platinium salts. Here, we analyze the efficacy and lack of toxicity of AsiDNA, a cholesterol form of Dbait, in hematologic malignancies. We show that AsiDNA, enters cells via LDL receptors and activates its molecular target, the DNA dependent protein kinase (DNA-PKcs) in 10 lymphoma and leukemia cell lines (Jurkat-E6.1, MT-4, MOLT-4, 174xCEM.T2, Sup-T1, HuT-78, Raji, IM-9, THP-1 and U-937) and in normal primary human PBMCs, resting or activated T-cells, and CD34+ progenitors. The treatment with AsiDNA induced necrotic and mitotic cell death in most cancer cell lines and had no effect on blood or bone marrow cells, including immune activation, proliferation or differentiation. Sensitivity to AsiDNA was independent of p53 status. Survival to combined treatment with conventional therapies (etoposide, cyclophosphamides, vincristine, or radiotherapy) was analyzed by isobolograms and combination index. AsiDNA synergized with all treatments, except vincristine, without increasing their toxicity to normal blood cells. AsiDNA is a novel, potent, and wide range drug with the potential to specifically increase DNA damaging treatment toxicity in tumor without adding toxicity in normal hematologic cells or inducing immune dysregulation.

Biau J., Chautard E., De Koning L., Court F., Pereira B., Verrelle P., Dutreix M. (2017 Jul 1)
Predictive biomarkers of resistance to hypofractionated radiotherapy in high grade glioma
RADIATION ONCOLOGY : 12 : 123: DOI : 10.1186/s13014-017-0858-0

Summary

Background: Radiotherapy plays a major role in the management of high grade glioma. However, the radioresistance of glioma cells limits its efficiency and drives recurrence inside the irradiated tumor volume leading to poor outcome for patients. Stereotactic hypofractionated radiotherapy is one option for recurrent high grade gliomas. Optimization of hypofractionated radiotherapy with new radiosensitizing agents requires the identification of robust druggable targets involved in radioresistance.
Methods: We generated 11 xenografted glioma models: 6 were derived from cell lines (1 WHO grade III and 5 grade IV) and 5 were patient derived xenografts (2 WHO grade III and 3 grade IV). Xenografts were treated by hypofractionated radiotherapy (6x5Gy). We searched for 89 biomarkers of radioresistance (39 total proteins, 26 phosphoproteins and 24 ratios of phosphoproteins on total proteins) using Reverse Phase Protein Array.

Results: Both type of xenografted models showed equivalent spectrum of sensitivity and profile of response to hypofractionated radiotherapy. We report that Phospho-EGFR/EGFR, Phospho-Chk1/Chk1 and VCP were associated to resistance to hypofractionated radiotherapy.

Conclusions: Several compounds targeting EGFR or CHK1 are already in clinical use and combining them with stereotactic hypofractionated radiotherapy for recurrent high grade gliomas might be of particular interest.

Charles Fouillade, Vincent Favaudon, Marie-Catherine Vozenin, Paul-Henri Romeo, Jean Bourhis, Pierre Verrelle, Patrick Devauchelle, Annalisa Patriarca, Sophie Heinrich, Alejandro Mazal, Marie Dutreix (2017 Mar 12)

[Hopes of high dose-rate radiotherapy].
Bulletin du cancer : DOI : S0007-4551(17)30031-0

Summary

In this review, we present the synthesis of the newly acquired knowledge concerning high dose-rate irradiations and the hopes that these new radiotherapy modalities give rise to. The results were presented at a recent symposium on the subject.