New DNA repair inhibitor Dbait in combination with radiation therapy to treat melanoma: a preclinical study

Julian Blau1,2, Flavien Devun1,2, Jian-Sheng Sun3, Pierre Verrelle2 and Marie Dutreix1
1Institut Curie, CNRS-UMR3347, INSERM-U1021, Université Paris-Sud, Orsay, France;
2Centre Jean Perrin, Clermond-Ferrand, France; 3DNA Therapeutics, Evry, France

Abstract

Background and purpose: Melanoma is radioresistant. The cytotoxicity of radiotherapy (RT) is mainly due to DNA double-strand breaks (DSB). Dbait is an innovative molecule which mimics DSB that turn DNA repair proteins and prevent their recruitment thereby inhibiting repair of RT-induced DNA damage. We assessed the efficacy and safety of combining RT with Dbait in a model of human melanoma.

Material and Methods: Initially, the cytotoxic efficacy of Dbait in combination with RT was evaluated in vitro. We further assessed the capacity of DT01 (clinical form of Dbait) to enhance radiation efficiency on a radioresistant human melanoma xenografted model (SK28). For this we monitored tumour growth and survival of nude mice subcutaneously engrafted with SK2 after treatment with Dbait, “paralytic” (100Gy) or “radial” (200Gy) RT, or a combination of Dbait and RT.

Results: In vitro, Dbait enhanced RT-induced cytotoxicity independently of RT doses (p<0.01). In Dbait and RT treated cells, initially the level of DNA damage was not greater than in RT treated cells, but damage persisted for longer (p<0.01) indicating a delay in their repair. Mice treated with DT01 and RT combination had significantly better tumor growth control and longer survival compared to RT alone with the same RT schedule (p<0.01) and the same protocol of the “radial” treatment (100Gy). Only animals that received the combined treatment showed complete responses. No additional toxicity was observed in any DT01-treated group.

Conclusions: This preclinical study provides encouraging results for a new DNA repair inhibitor, DT01, with RT, with no added toxicity in any DT01-treated group.

1. Introduction

DNA repair and cancer

Tumor cells survive genetic: Treatment by repairing DNA damage.

As enhanced DNA repair machinery is a main mechanism of resistance to treatment of metastatic and advanced-stage cancer, it is a potential target.

However, redundancy of DNA repair pathways makes full DNA repair inhibition difficult to achieve using single target inhibitors.

Dbait a global inhibitor

Dbait is a small double-stranded oligonucleotide recognized by two DNA break sensors PARP and DNA-PK.

By recruiting DNA repair enzymes, Dbait paralyzes the whole DNA repair machinery which is not able to detect DNA breaks anymore.

Repair foci do not form in Dbait treated cells

3. Tumor specific sensitization to RT

With palliative radiotherapy (10 x 3Gy)

Dbait combination to RT improves survival of nude mice xenografted with human melanoma (SK28). The activity is synergic with radiotherapy.

Moreover, addition of Dbait treatment one month after the first treatment (RT5+Dbait5) increases the efficacy.

It may be valuable to repeat Dbait administration regularly during the months that follow irradiation in area that cannot be irradiated anymore.

With radical radiotherapy (20 x 3Gy)

Ongoing Clinical trial

An open label, non-randomized, first-in-human, multi-centre phase I trial study to evaluate the safety, tolerability, pharmacokinetics and efficiency of locally administered DT01 in combination with radiotherapy in patients with melanoma-in-transit (supported by AHF and DNA Therapeutics).

4. Tumor sensitization to radiotherapy

Predictional model of SK28 human melanoma xenografted in mouse

Conclusion

• Dbait is a tool that activates DNA-PK and PARP-dependent damage signaling
• DNA-PK and PARP activation leads to inhibition of DNA repair proteins recruitment at damage site
• The perturbation of the DNA-damage response leads to the inhibition of DNA repair and sensitizes cells to ionizing radiation
• Dbait sensitizes tumors to radiotherapy
• DT01, a cholesterol derivative of Dbait, has no effect on healthy tissues and specifically sensitizes tumors to irradiation.

Dbait is a good candidate for improving radiotherapy and chemotherapy efficiency without adding toxicity

5. DRIIM: 1st-in-human trial in melanoma-in-transit (NCT01469455)

• No need of potentially toxic vector (recombinant in 95% glucose or saline solution)
• Optimized and encapsulated CMC (< 12% full-length purity)
• Stable = 2 years in hypothermia (2012)

Distribution and radiosensitizing effect of cholesterol-Dbaite in combination with RT (10x 3Gy)