Année de publication : 2019

Charles Fouillade, Sandra Curras-Alonso, Lorena Giuranno, Eddy Quelennec, Sophie Heinrich, Sarah Bonnet-Boissinot, Arnaud Beddok, Sophie Leboucher, Hamza Umut Karakurt, Mylène Bohec, Sylvain Baulande, Marc Vooijs, Pierre Verrelle, Marie Dutreix, Arturo Londoño-Vallejo, Vincent Favaudon (2019 Dec 5)

FLASH Irradiation Spares Lung Progenitor Cells and Limits the Incidence of Radio-induced Senescence.

Clinical cancer research : an official journal of the American Association for Cancer Research : DOI : 10.1158/1078-0432.CCR-19-1440

Résumé

One of the main limitations to anticancer radiotherapy lies in irreversible damage to healthy tissues located within the radiation field. « FLASH » irradiation at very high dose-rate is a new treatment modality that has been reported to specifically spare normal tissue from late radiation-induced toxicity in animal models and therefore could be a promising strategy to reduce treatment toxicity.

Nirmitha I Herath, Nathalie Berthault, Sylvain Thierry, Wael Jdey, Marie-Christine Lienafa, Françoise Bono, Patricia Noguiez-Hellin, Jian-Sheng Sun, Marie Dutreix (2019 Nov 30)

Preclinical Studies Comparing Efficacy and Toxicity of DNA Repair Inhibitors, Olaparib, and AsiDNA, in the Treatment of Carboplatin-Resistant Tumors.

Frontiers in oncology : 1097 : DOI : 10.3389/fonc.2019.01097

Résumé

Carboplatin is used to treat many cancers, but occurrence of drug resistance and its high toxicity remain a clinical hurdle limiting its efficacy. We compared the efficacy and toxicity of DNA repair inhibitors olaparib or AsiDNA administered alone or in combination with carboplatin. Olaparib acts by inhibiting PARP-dependent repair pathways whereas AsiDNA inhibits double-strand break repair by preventing recruitment of enzymes involved in homologous recombination and non-homologous end joining. Mice with MDA-MB-231 tumors were treated with carboplatin or/and olaparib or AsiDNA for three treatment cycles. Survival and tumor growth were monitored. Toxicities of treatments were assayed in C57BL/6 immunocompetent mice. Circulating blood hematocrits, bone marrow cells, and organs were analyzed 10 and 21 days after end of treatment using flow cytometry and microscopy analysis. Resistance occurrence was monitored after cycles of treatments with combination of AsiDNA and carboplatin in independent BC227 cell cultures. Olaparib or AsiDNA monotherapies decreased tumor growth and increased mean survival of grafted animals. The combination with carboplatin further increased survival. Carboplatin toxicity resulted in a decrease of most blood cells, platelets, thymus, and spleen lymphocytes. Olaparib or AsiDNA monotherapies had no toxicity, and their combination with carboplatin did not increase toxicity in the bone marrow or thrombocytopenia. All animals receiving carboplatin combined

with olaparib developed high liver toxicity with acute hepatitis at 21 days. , carboplatin resistance occurs after three cycles of treatment in all six tested cultures, whereas only one became resistant (1/5) after five cycles when carboplatin was associated to low doses of AsiDNA. All selected carboplatin-resistant clones retain sensitivity to AsiDNA. DNA repair inhibitor treatments are efficient in the platinum resistant model, MDA-MB-231. The combination with carboplatin improves survival. The association of carboplatin with olaparib is associated with high liver toxicity, which is not observed with AsiDNA. AsiDNA could delay resistance to carboplatin without increasing its toxicity.

Julian Biau, Emmanuel Chautard, Pierre Verrelle, Marie Dutreix (2019 Oct 26)
Altering DNA Repair to Improve Radiation Therapy: Specific and Multiple Pathway Targeting.
Frontiers in oncology : 1009 : DOI : 10.3389/fonc.2019.01009

Résumé

Radiation therapy (RT) is widely used in cancer care strategies. Its effectiveness relies mainly on its ability to cause lethal damage to the DNA of cancer cells. However, some cancers have shown to be particularly radioresistant partly because of efficient and redundant DNA repair capacities. Therefore, RT efficacy might be enhanced by using drugs that can disrupt cancer cells' DNA repair machinery. Here we review the recent advances in the development of novel inhibitors of DNA repair pathways in combination with RT. A large number of these compounds are the subject of preclinical/clinical studies and target key enzymes involved in one or more DNA repair pathways. A totally different strategy consists of mimicking DNA double-strand breaks via small interfering DNA (siDNA) to bait the whole DNA repair machinery, leading to its global inhibition.

Wael Jdey, Maria Kozlak, Sergey Alekseev, Sylvain Thierry, Pauline Lascaux, Pierre-Marie Girard, Françoise Bono, Marie Dutreix (2019 Jul 31)
AsiDNA Treatment Induces Cumulative Antitumor Efficacy with a Low Probability of Acquired Resistance.
Neoplasia (New York, N.Y.) : 863-871 : DOI : S1476-5586(19)30213-1

Résumé

The Achilles heel of anticancer treatments is intrinsic or acquired resistance. Among many targeted therapies, the DNA repair inhibitors show limited efficacy due to rapid emergence of resistance. We examined evolution of cancer cells and tumors treated with AsiDNA, a new DNA repair inhibitor targeting all DNA break repair pathways. Effects of AsiDNA or Olaparib were analyzed in various cell lines. Frequency of AsiDNA- and olaparib-resistant clones was measured after 2 weeks of continuous treatment in KBM7 haploid cells. Cell survivals were also measured after one to six cycles of 1-week treatment and 1-week recovery in MDA-MB-231 and NCI-H446. Transcriptomes of cell populations recovering from cyclic treatments or mock treatment were compared. MDA-MB-231 xenografted models were treated with

three cycles of AsiDNA to monitor the effects of treatment on tumor growth and transcriptional modifications. No resistant clones were selected after AsiDNA treatment (frequency < 3×10) in treatment conditions that generate resistance to olaparib at a frequency of 7.2×10 resistant clones per treated cell. Cyclic treatments promote cumulative sensitivity characterized by a higher mortality of cells having undergone previous treatment cycles. This sensitization was stable, and transcriptome analysis revealed a major gene downregulation with a specific overrepresentation of genes coding for targets of DNA-PK. Such changes were also detected in tumor models which showed impaired growth after cycles of AsiDNA treatment.

Julian Biau, Emmanuel Chautard, Nathalie Berthault, Leanne de Koning, Frank Court, Bruno Pereira, Pierre Verrelle, Marie Dutreix (2019 Jul 6)

Combining the DNA Repair Inhibitor Dbait With Radiotherapy for the Treatment of High Grade Glioma: Efficacy and Protein Biomarkers of Resistance in Preclinical Models.

Frontiers in oncology : 549 : DOI : 10.3389/fonc.2019.00549

Résumé

High grade glioma relapses occur often within the irradiated volume mostly due to a high resistance to radiation therapy (RT). Dbait (which stands for DNA strand break bait) molecules mimic DSBs and trap DNA repair proteins, thereby inhibiting repair of DNA damage induced by RT. Here we evaluate the potential of Dbait to sensitize high grade glioma to RT. First, we demonstrated the radiosensitizer properties of Dbait in 6/9 tested cell lines. Then, we performed animal studies using six cell derived xenograft and five patient derived xenograft models, to show the clinical potential and applicability of combined Dbait+RT treatment for human high grade glioma. Using a RPPA approach, we showed that Phospho-H2AX/H2AX and Phospho-NBS1/NBS1 were predictive of Dbait efficacy in xenograft models. Our results provide the preclinical proof of concept that combining RT with Dbait inhibition of DNA repair could be of benefit to patients with high grade glioma.

Année de publication : 2018

Annalisa Patriarca, Charles Fouillade, Michel Auger, Frédéric Martin, Frédéric Pouzoulet, Catherine Nauraye, Sophie Heinrich, Vincent Favaudon, Samuel Meyroneinc, Rémi Dendale, Alejandro Mazal, Philip Poortmans, Pierre Verrelle, Ludovic De Marzi (2018 Nov 1)

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

International Journal of Radiation Oncology • Biology • Physics : 102 : 619-626 : DOI : 10.1016/j.ijrobp.2018.06.403

Résumé

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 mm^2 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.

Marie-Catherine Vozenin, Pauline De Fornel, Kristoffer Petersson, Vincent Favaudon, Maud Jaccard, Jean-François Germond, Benoit Petit, Marco Burki, Gisèle Ferrand, David Patin, Hanan Bouchaab, Mahmut Ozsahin, François Bochud, Claude Bailat, Patrick Devauchelle, Jean Bourhis (2018 Jun 8)

The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients.

Clinical cancer research : an official journal of the American Association for Cancer Research : 35-42 : DOI : 10.1158/1078-0432.CCR-17-3375

Résumé

Previous studies using FLASH radiotherapy (RT) in mice showed a marked increase of the differential effect between normal tissue and tumors. To stimulate clinical transfer, we

evaluated whether this effect could also occur in higher mammals.

Année de publication : 2017

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

Résumé

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

Résumé

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.

Pierre Montay-Gruel, Kristoffer Petersson, Maud Jaccard, Gaël Boivin, Jean-François Germond, Benoit Petit, Raphaël Doenlen, Vincent Favaudon, François Bochud, Claude Bailat, Jean Bourhis, Marie-Catherine Vozenin (2017 May 27)

Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100Gy/s.

Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology : 365-369 : DOI : S0167-8140(17)30365-1

Résumé

This study shows for the first time that normal brain tissue toxicities after WBI can be reduced with increased dose rate. Spatial memory is preserved after WBI with mean dose rates above 100Gy/s, whereas 10Gy WBI at a conventional radiotherapy dose rate (0.1Gy/s) totally impairs spatial memory.

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

Résumé

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.

Marie Dutreix, Michel Marty (2017 Jan 15)
[La Société Française du Cancer is moving forward].
Bulletin du cancer : 2-3 : DOI : S0007-4551(16)30366-6

Résumé

Année de publication : 2016

Julian Biau, Emmanuel Chautard, Frank Court, Bruno Pereira, Pierre Verrelle, Flavien Devun, Leanne De Koning, Marie Dutreix (2016 Aug 29)
Global Conservation of Protein Status between Cell Lines and Xenografts.
Translational oncology : 313-321 : DOI : S1936-5233(16)30044-4

Résumé

Common preclinical models for testing anticancer treatment include cultured human tumor cell lines in monolayer, and xenografts derived from these cell lines in immunodeficient mice. Our goal was to determine how similar the xenografts are compared with their original cell line and to determine whether it is possible to predict the stability of a xenograft model beforehand. We studied a selection of 89 protein markers of interest in 14 human cell cultures and respective subcutaneous xenografts using the reverse-phase protein array technology. We specifically focused on proteins and posttranslational modifications involved in DNA repair, PI3K pathway, apoptosis, tyrosine kinase signaling, stress, cell cycle, MAPK/ERK signaling, SAPK/JNK signaling, NFκB signaling, and adhesion/cytoskeleton. Using hierarchical clustering, most cell culture-xenograft pairs cluster together, suggesting a global conservation of protein signature. Particularly, Akt, NFkB, EGFR, and Vimentin showed very stable protein expression and phosphorylation levels highlighting that 4 of 10 pathways were highly correlated whatever the model. Other proteins were heterogeneously conserved depending on the cell line. Finally, cell line models with low Akt pathway activation and low levels of Vimentin gave rise to more reliable xenograft models. These results may be useful for the extrapolation of cell culture experiments to in vivo models in novel targeted drug discovery.

Wael Jdey, Sylvain Thierry, Christophe Russo, Flavien Devun, Muthana Al Abo, Patricia Noguiez-Hellin, Jian-Sheng Sun, Emmanuel Barillot, Andrei Zinovyev, Inna Kuperstein, Yves Pommier, Marie Dutreix (2016 Aug 26)
Drug Driven Synthetic Lethality: bypassing tumor cell genetics with a combination of Dbait and PARP inhibitors.
Clinical cancer research : an official journal of the American Association for Cancer Research :
DOI : clincanres.1193.2016

Résumé

Cancer treatments using tumor defects in DNA repair pathways have shown promising results but are restricted to small subpopulations of patients. The most advanced drugs in this field are Poly(ADP-Ribose) Polymerase (PARP) inhibitors (PARPi), which trigger synthetic lethality in tumors with Homologous Recombination (HR) deficiency. Using AsiDNA, an inhibitor of HR and Non Homologous End Joining, together with PARPi should allow bypassing the genetic restriction for PARPi efficacy.

Marie Dutreix, Michel Marty (2016 Aug 7)
[Not Available].
Bulletin du cancer : S3 : DOI : 10.1016/S0007-4551(16)30139-4

Résumé