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Editorial

Authors' View—FLASH Radiation: A Game-Changer in Pediatric Brain Tumor Treatment?

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Introduction

Recent advances in cancer treatment have sought to refine therapeutic approaches to improve efficacy while minimizing toxicity. FLASH radiation therapy (FLASH RT) is an ultrahigh dose rate radiation therapy technique that has garnered attention for its ability to decrease normal tissue toxicity while maintaining the therapeutic efficacy of conventional RT. Although conventional RT is delivered as dose rates of approximately 0.1 Gy per second, FLASH RT generally refers to RT delivered at 40 Gy per second or faster. FLASH RT dose rates can be achieved by electron beams, and now by proton, photon, and even carbon ion beams. By delivering radiation at ultrahigh dose rates, FLASH RT has shown promise in reducing side effects associated with standard radiation therapy, potentially widening the therapeutic window for oncology treatments. Our recent study published in *Nature Cancer* by Ni et al[1] offers a tantalizing perspective on FLASH RT, demonstrating its potential to revolutionize the treatment of medulloblastoma through

metabolic reprogramming and enhanced immunotherapy responsiveness. This Authors' View highlights the findings from this research and their broader implications for pediatric oncology.

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Section snippets

The Challenge of Medulloblastoma Treatment

Medulloblastoma, the most common malignant brain tumor in children, remains a formidable clinical challenge. Despite aggressive multimodal treatment, outcomes for high-risk cases remain dismal, necessitating novel therapeutic strategies. For survivors, neurotoxicity from a treatment paradigm that includes craniospinal RT with a tumor bed boost is a considerable long-term problem. Immunotherapy, particularly chimeric antigen receptor (CAR)-T cell therapy, has shown promise in hematologic …

FLASH RT in Brain Tumors: Advancing the Field

Significant work has been done on the effects of FLASH RT specifically in normal brain and brain tumor models. A reinvigoration of interest in the FLASH effect occurred in 2014, when Favaudon et al[2] showed considerably decreased lung fibrosis with electron FLASH RT beams in lung cancer allograft mouse models, but equivalent tumor control to conventional RT. Montay-Gruel et al[3] extended this work into the brain tumor space, for instance demonstrating that electron FLASH RT reduces neurocognitive …

FLASH RT and Immune Modulation

Previous research has provided foundational insights into the immune-modulatory effects of FLASH RT. For example, computational modeling by Jin et al[5] predicted that FLASH RT may expose fewer circulating immune cells to lethal doses of RT compared with conventional RT, potentially contributing to its normal tissue-sparing effects. Katsuki et al[6] provided evidence that carbon ion FLASH RT may downregulate immune checkpoint protein expression on cancer cells, enhancing their immunogenicity and …

Studying the FLASH Effect in a Primary Mouse Model

Ni et al[1] advance our understanding of the FLASH RT effect by exploring its interaction with the immune system in pediatric brain tumors. We used a genetically engineered mouse model in

which tumors develop spontaneously in fully immune-competent mice. This approach allows for the study of FLASH RT in a tumor microenvironment that naturally coevolves with the immune system—unlike graft-based models, which may alter tumor characteristics such as hypoxia, immune interactions, and radiation …

FLASH and Lipid Metabolism: A Mechanistic Breakthrough

To investigate potential unique effects of FLASH RT on the tumor immune microenvironment in primary brain tumors, we began by performing single-cell transcriptomic analysis. This analysis revealed that FLASH RT induces a shift in tumor-associated macrophages toward proinflammatory phenotypes. This contrasted sharply with the more immunosuppressive macrophage states observed after conventional RT. Guided by these observations, we identified a reduction in the expression of arginase 1 (*Arg1*) and …

FLASH to Stimulate Immunotherapy

These changes created a microenvironment more amenable to immune attack. Inspired by the proinflammatory changes induced by FLASH RT, we tested if FLASH RT could stimulate CAR-T cell therapy. We used CARs directed at the GD2 antigen, a disialoganglioside expressed on the surface of medulloblastoma cells. FLASH RT significantly improved CAR-T cell infiltration, activation, and therapeutic efficacy relative to conventional RT. The combination outperformed standard RT plus CAR-T therapy, offering …

Future Directions and Clinical Translation

From a translational perspective, the implications of these findings are profound. By mitigating radiation-induced normal tissue damage while simultaneously amplifying antitumor immunity, FLASH RT represents a paradigm shift in radiation therapy for pediatric brain tumors (Fig. 2). The study demonstrates that combining FLASH RT with GD2 CAR-T therapy extends survival in preclinical models, positioning this approach as a highly promising avenue for clinical translation.

Despite these promising …

Conclusion

The intersection of radiation oncology and immunotherapy is an exciting frontier in cancer treatment. This study underscores the potential of FLASH RT to redefine the therapeutic landscape for medulloblastoma by overcoming the limitations of standard RT and unlocking the full potential of CAR-T cell therapy. As we move toward clinical application, the integration of FLASH RT into pediatric neuro-oncology protocols holds the promise of significantly improving outcomes for children with high-risk …

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There are more references available in the full text version of this article.

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