FLASH Radiotherapy—Radiobiological Rationale

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FLASH radiotherapy, or the administration of ultra-high dose rate radiotherapy, is a new radiation delivery method that aims to widen the therapeutic window in radiotherapy through better sparing of the normal tissue.

Keywords: FLASH-radiotherapy ; FLASH-radiobiology ; therapeutic window

1. Introduction

FLASH radiotherapy is a non-conventional technique that delivers dose rates ≥ 40 Gy/s for a single radiation dose [1]. While the biological mechanisms behind FLASH are not fully elucidated, the scientific rationale behind the administration of ultra-high dose rates is the enhancement of the therapeutic window in radiation therapy through a better normal tissue sparing and similar, or an increased, tumour control, as compared to conventional therapies [2].

2. Radiobiological Rationale

To date, the radiobiology of FLASH radiation therapy is not fully understood. In most references, this is explained by: (a) oxygen depletion effect, (b) inflammatory processes, (c) redox biology, and (d) differential effect/reaction of normal vs. tumour tissues [2][3][4][5].

Oxygen depletion is considered to have radio-protective effect on normal tissues. Once the oxygen levels have been depleted sufficiently by the initial boost of radiation, the subsequent irradiation of normal tissues occurs in hypoxic conditions, and therefore in a radioresistant state. Additionally, when using high doses and ultra-high dose rates, reoxygenation cannot occur. This may, in effect, separate the window between tumour control probability (TCP) and normal tissue complication probability (NTCP) curves [2].

This is possibly an overly simplistic explanation, and doubts persist as to whether the dose rates used clinically in FLASH radiotherapy are sufficient to significantly affect radiolysis yields. Considering the many biological processes occurring at the subcellular level during irradiation, other processes may be responsible for the clinical effects observed, including chromatin remodelling or inflammatory/anti-inflammatory cell signalling [3].

To illustrate the role played by oxygen depletion in the FLASH effect, a recent in vitro study compared FLASH irradiation (600 Gy/s dose rate) and conventional radiotherapy (14 Gy/min dose rate) under various oxygen concentrations [6]. This study was undertaken on prostate cancer cells, irradiated with a 10 MeV electron beam under various oxygenation conditions, with the relative partial oxygen pressure ranging between 16–20%. Surviving fractions via clonogenic assays were determined after exposure to doses up to 25 Gy. The results showed no difference between the two techniques under normoxic conditions, nor under hypoxia up to 5–10 Gy radiation dose. However, above this dose range, cells irradiated with FLASH presented an increased survival, dependent on oxygen concentration, which became significant at 18 Gy. This study provides in vitro evidence supporting the oxygen dependence of FLASH effects.

A molecular dynamics simulation was performed by Abolfarth et al. [7] to study the production and interaction of reactive species around DNA for varying dose rates and oxygenation levels. In normoxic conditions at high dose rates, it was found that individual reactive oxygen species (ROS) agglomerated to form resonant or meta-stable molecular states connected by hydrogen bonds. The resulting agglomerations have a low diffusion capability and are hence non-reactive oxygen species (NROS) with limited potential for biological damage. The production of NROS was found to be reduced at lower dose rates and in hypoxic conditions resulting in a higher proportion of free ROS. It was proposed that high oxygenation levels would saturate the agglomeration process, leading ROS to again be dominant over NROS. The observed agglomeration and resulting protection of normoxic tissues at high dose rates is a potential advantage of the observed FLASH effect.

Petersson et al. [8] developed a model of oxygen depletion kinetics and the resulting oxygen enhancement ratio. It was found that the oxygen enhancement ratio was reduced for higher doses and dose-rates. The model was tested against experimental data and was able to reproduce the observed results supporting the oxygen depletion explanation of the FLASH effect.

Kusumoto et al. [9] performed an experiment to measure the yield of hydroxyl radicals for a range of dose rates using coumarin-3-carboxylic acid as a hydroxyl radical scavenger. The yield of the hydroxyl radical was found from the measured yield of 7-hydroxy-coumarin-3-carboxylic acid produced from the scavenging reactions. It was found that the hydroxyl radical yield was reduced for higher dose rates. It was proposed that the reduction in yield was the result of oxygen depletion and that the reduced yield would result in decreased indirect biological damage.

Other research suggests that FLASH therapy reduces long-term radiation effects (i.e., not the immediate cell kill), thus diminishing the side effects experienced by normal tissues post irradiation [4]. This is hypothesized to be due to reduced cell senescence, linked to the release of pro-inflammatory cytokines, with inflammatory processes remaining active in subsequent progeny for several generations. As such, decreased cell senescence indicates an overall decline in various inflammatory responses of normal tissues [4].

Jay-Gerin [10] demonstrated with Monte Carlo simulations that at the high dose rates of FLASH therapy the transient acid spikes around the path of each incident radiation particle combine to result in acidic conditions across the entire irradiated volume. It was proposed that these acidic conditions could contribute to the observed FLASH effect. Jin et al. [11] presented a computational study showing that higher dose rates reduced the proportion of circulating cells in the blood stream that were irradiated, particularly for higher doses. It was proposed that the increased sparing of circulating immune cells could contribute to the FLASH effect.

A chemical reaction kinetics model was employed by Labarbe et al. [12] to simulate the formation and decay of ROS following irradiation. It was found that the dose rate and oxygenation level had a strong effect on the lifetime of organic peroxyl radicals. At moderate oxygenation levels, higher dose rates reduced the lifetime of the organic peroxyl radicals and hence the potential biological damage. The reduction in the radical lifetime was specific for both hypoxic and high oxygenation levels. This provides a potential cause of the observed FLASH effect that does not involve oxygen depletion.

Following radiation exposure, it is the redox biology specific to normal and cancerous cells that controls the recovery from radiation damage [13]. The different redox metabolism and observed altered steady-state levels of ROS and redox metals (such as labile iron) in cancer cells, mean that normal cells can eliminate free radicals produced during irradiation more effectively [14]. Spitz et al. propose that cancer cells contain much higher levels of labile iron and transferrin receptors, resulting in magnification of Fenton reactions, catalytic processes that convert hydrogen peroxide to hydroxyl free radicals, potentially resulting in much higher oxidative damage in cancer compared to normal cells [14]. Normal cells, however, contain less labile iron and are capable of faster removal of the FLASH-induced hydroperoxides, limiting peroxidation chain reactions [14].

As a result, evidence has been put forward that the major benefit of FLASH is its reduced toxicity on normal tissues, known as the “FLASH-effect” [15]. At the same time, the literature suggests that cell-kill efficacy of FLASH is equal to conventional dose rate radiotherapy, supporting the net effect of separating the TCP and NTCP curves [15].

While some of the fundamental radiobiological processes are understood or hypothesised, much deeper understanding of FLASH-associated radiation chemistry and cellular processes is required for a safe clinical employment. Moreover, in order to implement this treatment modality scientifically, rather than phenomenologically or solely based on observations, it is important to understand the challenges imposed by FLASH to other concepts that are broadly accepted in radiation biology such as the 5 Rs [16].

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