



Short Communication

Comparison of ultra-high versus conventional dose rate radiotherapy in a patient with cutaneous lymphoma



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ABSTRACT

A patient with a cutaneous lymphoma was treated on the same day for 2 distinct tumors using a 15 Gy single electron dose given in a dose rate of 0.08 Gy/second versus 166 Gy/second. Comparing the two treatments, there was no difference for acute reactions, late effects at 2 years and tumor control.

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Ultra-high dose rate radiotherapy (RT), also described as FLASH-radiotherapy [1] delivers RT in milliseconds and has been associated in pre-clinical studies with less side effects on healthy tissues, when compared to conventional dose rate RT (CONV) delivered in minutes, while the effect on tumors appeared similar. The consistency of the phenomenon across tissues and species along with the magnitude of the effect appeared promising, and prompted for its clinical translation [5,6]. Indeed, ultra-high dose rate could allow to deliver higher doses to the tumors and enlarge the therapeutic window of RT [1–5,8–10].

Translating this observation in a clinical setting is starting to be investigated [6], with a need to combine overall delivery time of time in milliseconds with high precision radiation delivery that generally requires multiple angles and multiple beams for optimal dose distribution. Another key aspect is to understand what could be the optimal fractionation for these FLASH treatments. Indeed, the healthy tissues sparing effect has been mostly observed with high single doses (above 6–7 Gy) [1–5,8–10] and little is known about the FLASH effect in more conventional fractionated RT [7,9].

More than 2 years ago, we reported the feasibility and safety of a first ultra-high dose rate FLASH treatment in a patient with

refractory cutaneous lymphoma [6]. This patient was subsequently treated for two additional tumors, one with ultra-high dose rate (FLASH), one with conventional dose rate (CONV). We report here the outcome of these 2 treatments.

Material and methods

Following approval from the Federal Office of Public Health (OFSP) and clinical ethical committee approval, a 75-year-old patient with a multiply relapsed cutaneous T-cell lymphoma [6] was treated in the frame of our Hospital Directive DIM DI 0112 and after receiving his informed consent. The patient had an extensive history of skin RT as previously described [6]. On the same day he was irradiated for two cutaneous tumors, both located in previously unirradiated sites. The first tumor was measuring 2.8×2.7 cm located on the inner side of right elbow with CONV and the second one 4.2×3.4 cm located on the posterior part of the distal left arm with FLASH. CONV was given with a 8-MeV electron beam (Synergy Elekta, Crawley, UK) and a 1.2-cm bolus, while FLASH was given with a 5.6-MeV linac (Oriatron, Alcen-PMB, France) with a 0.5-cm bolus. Due to the multiple relapsing nature of this lymphoma, a dose of 15 Gy to the PTV was selected and prescribed at the depth of maximum dose for both tumors, given in 2.87 minutes for CONV (mean dose rate 0.087 Gy/s) versus in 90 ms for FLASH (10 pulses of 1 μ s at 100 Hz, mean dose rate 166 Gy/s and

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instantaneous dose rate 1.5×10^6 Gy/s)). The source skin distance (SSD) was 65 cm for FLASH and 100 cm for CONV. In both cases, the total depth covered by the 95% isodose was about 1.3 cm, taking into account the thickness of the tumor, the energy and the thickness of the bolus. Due to the difference of tumor size and shape, the planned target volumes (PTVs) were estimated at 17.6 cc for CONV versus 21.6 cc for FLASH.

Redundant dosimetric checks were performed before and after the treatment in conditions mimicking the treatment, as previously described [6,11,12], using GafChromic films for measuring dose profiles and alanine pellets for the absolute dose measurement at the center of the beam. These dosimetric checks were completed during the treatment by positioning alanine pellets at the inner limit of the PTV under the bolus. That dosimetric process ensured that the PTV coverage was at least 95% of the prescribed dose.

During the first 3 months following RT, acute reactions were clinically monitored initially on a weekly basis and after 1 month on a bi-weekly basis using CTCAE v5 scoring system. Photographs were taken at the peak of skin reactions and were subsequently reviewed by 3 physicians (2 radiation oncologists and one dermatologist) who were blinded to the type of treatment received by the patient.

Late effects were evaluated at 24 months through clinical evaluation, photographs and skin biopsies. The pathological examinations were performed by a pathologist who was blinded to the type of treatment received by the patient. Local skin was also analyzed by non-invasive microscopy using an VivoSightDx (Michelson Diagnostics, UK) multi-beam optical coherence tomograph, capturing 6x6-mm scans with a 6- μ m resolution of the skin, up to a depth of 2 mm. This imaging technique allows to precisely measure epidermal and dermal thickness.

Results

The dose measured by *in vivo* dosimetry with alanine pellet was 14.7 ± 0.5 Gy for FLASH and 14.4 ± 0.5 Gy for CONV in 95% of the PTV.

Following both FLASH and CONV, an erythema was observed in the irradiated field on the skin surrounding the tumor with a maximal reaction around 3 weeks after treatment, consisting of mild epithelitis (grade 1 according to NCI-CTCAE v 5.0, Fig. 1). Clinical examination showed that the onset of grade 1 toxicity started on Day 10 both for FLASH and CONV, peaked around week 3 and 4 (Fig. 1 A and B at 17 days) while the disappearance of the grade 1 (return to a normal skin appearance) was in both cases observed at day 85. In both cases, the tumor disappeared with comparable kinetics and did not regrow after 24 months (Fig. 1C).

For late assessment at 24 months, in both cases, the general appearance of the skin in the irradiated field was qualified as normal. This was confirmed by optical coherence tomography scans which were used first to assess the general aspect of the skin, which appeared normal in both cases. There was a lack of skin appendages compatible with a physiological lack of these structures for the skin localizations and age of the patient. Epidermal thickness was slightly higher on the FLASH site than the CONV site. Multiple measures of epidermal thickness taken at pre-determined 100- μ m intervals on two adjacent scans confirmed this analysis, being 0.13 mm (SD \pm 0.01) for CONV and 0.15 mm (SD \pm 0.01) for FLASH, respectively. As a common late side effect of RT is epidermal thinning, this may suggest that CONV was less favorable. However, the depth of normal skin of a healthy volunteer matched the skin site, being 0.13 mm for the internal side of the left elbow, and 0.14 mm for the external side of the right elbow (data not shown). To assess the dermal fitness, the depth of the superficial

vascular plexus was measured, as we had previously observed that it is generally diminished in areas displaying severe signs of chronic radiodermatitis (from previous RT). This depth was measured at 0.38 mm (SD \pm 0.05) CONV and 0.49 mm (SD \pm 0.06) FLASH and was thus comparable in both cases, when accounting for differences in the localization (internal vs external side of the elbow). We concluded from this analysis that the level of late skin reactions was not clinically different between FLASH and CONV.

Skin biopsies revealed a mild chronic skin radiodermatitis with a minimal vacuolisation of the basal cell membrane, a hyalinisation of the vessels, a decrease of elastin along with increased collagen deposit (coloration Van-Gierson) in the superficial derm (Fig. 2). The thickness of the epidermis was normal but there was no epidermal digitation and absence of skin appendices (consistent with OCT). The pathologist (blinded for the CONV vs FLASH site, but knowing that both areas had been treated with RT) was unable to find a difference between the two biopsies, and evoked a similar level of mild radiodermatitis.

Discussion

This observation is a first direct comparison of ultra-high versus conventional dose rate in a human patient. The overall treatment time (90 ms versus 2.87 min) and the pulse structure (dose per pulse, duration of the pulse and number of pulses) were very different between FLASH and CONV. Regarding the other irradiation parameters, the measured doses were comparable and the penetration in depth of the beam (after correction with a bolus) adjusted to the shape and the thickness of the tumor were also comparable. The energy used was slightly different (5.6 MeV, versus 8 MeV, however with limited expected impact on a potential FLASH effect, since it has been observed with electron beams of various energies, ranging from 4 MeV to 17 MeV [12,13]).

However, due to a difference in tumor size and shape, the PTV was slightly higher for FLASH (4 cc higher), but it is a relatively small difference unlikely to have a marked impact on the observed skin reactions.

The ultra-high dose rate parameters used of 1.5 Gy per pulse of 1 μ s with a repetition rate of 100 Hz were very close to those previously shown to produce a biological "FLASH sparing" of healthy tissues in pre-clinical experiments [1–5,7–10], especially a skin sparing effect [4,13] and the same also as the ones previously reported in this patient [6]. With these parameters, no unexpected acute and late severe toxicity occurred, and the safety of this ultra-high dose rate radiotherapy was confirmed.

The skin reactions were mild, but nevertheless detectable both for acute (erythema) and late reactions (mild chronic dermatitis on skin biopsies) and there was no suggestion of a difference between FLASH and CONV, both for these acute and late effects. One of the strengths of this study is the methodology used with careful assessment and blinded review of some tangible endpoints (photographs and pathology). A long-term follow-up is also reported for the first time in a patient after a FLASH treatment.

Based on the data, the effects of FLASH and CONV appeared similar, but due to the limitations of this study (case report nature, only a single dose level used and no possibility for statistical testing of a null hypothesis) it is not possible to rule out that the effects of the two types of treatment might still be different.

Although there was no difference between FLASH and CONV at 15 Gy, this observation remains compatible with previous pre-clinical studies, which showed in animals a major sparing of normal healthy skin with FLASH, especially from severe late effects of radiation on the skin of the pig [4]. Indeed, the sparing effect regarding the late radiation-induced skin necrosis and the magnitude of the FLASH benefit were striking but observed at much



Fig. 1. Clinical examination showing the skin appearance before treatment (A) and at Day 17 (B) both for FLASH and CONV. In both cases, the tumor disappeared with comparable kinetics and did not regrow after 24 months (C).

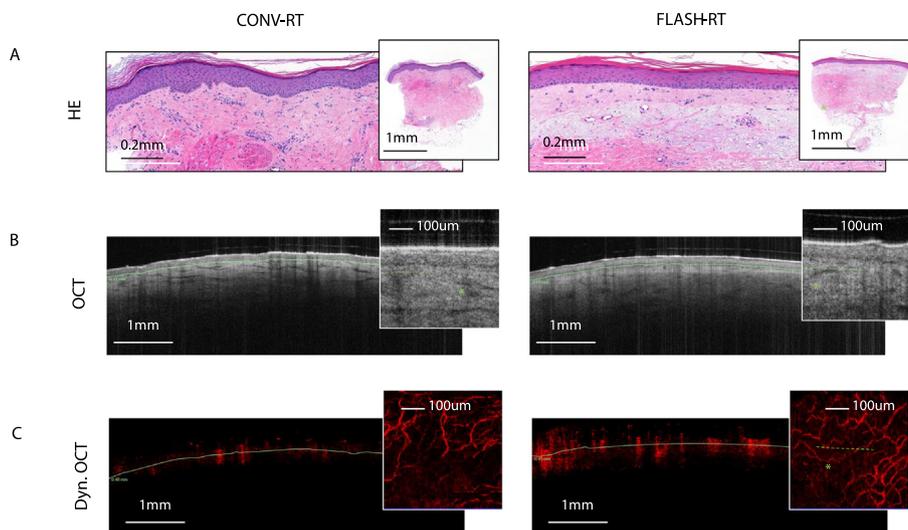


Fig. 2. Histologic and multi-beam optical coherence tomograph analysis of 2 years after CONV vs FLASH-RT. A) Hematoxylin-Eosin (HE) stain of punch biopsies. The inserts show the overall aspect of the biopsy, reaching the sub-cutis. The HE staining reveals a normal epidermis, a dermis devoid of skin adnexes, which is normal for the localisation and age, and a slight horizontalisation of the collagen bundles, with mild peri-vascular infiltrate, suggestive of mild chronic-radiodermatitis. B) Non-invasive imaging using OCT showing an essentially normal skin for the localisation and age. A slight epidermal thinning is noticed in the CONV-RT. The inserts show a close-up, where the junction is better seen. Green asterisk highlights a typical dermal blood vessel of the superficial vascular plexus. Lymphatic vessels may have a largely similar appearance in this mode. C) Non-invasive imaging using OCT in Dynamic Mode. This mode reveals blood flow in small blood vessels, excluding lymphatic vessels. The green line is set at the depths of the superficial vascular plexus and represents the level at which the insert's horizontal planar image is extracted. This insert shows the shape of the superficial vascular plexus in the horizontal plane. Scales are indicated in each panel either in mm or µm, as indicated.

higher dose levels in the range of 28–34 Gy single dose (in volumes slightly smaller but relatively close to the ones used in our patient) [4]. Our observation is also compatible with another comparison of electron beam FLASH versus CONV skin irradiation in mice. Indeed, Soto et al. [13] in a dose–response study showed a marked reduction of severe acute skin toxicity with FLASH versus CONV, which started to be detectable at 30 Gy single dose, whereas at lower dose levels (16 Gy for example), the difference between FLASH and CONV were relatively minimal which is in agreement with our study. Similarly, both Cunningham et al. [14] and Sorensen et al [15] reported a FLASH sparing effect on the skin of mice irradiated with a FLASH high single-dose proton beam (35 Gy and 24–50 Gy respectively) compared to similar doses with conventional proton beam. This suggests that at a lower dose level, such as the one used in our patient, a clinical difference between FLASH and CONV is likely hard to be detectable. Whilst this might be true, it would significantly limit the potential utility of FLASH. Future clinical assessment of ultra-high dose rate radiotherapy including direct comparison with conventional dose rates has been initiated in our institute, along with a dose escalation clinical trial (IMPULSE, NCT 04592887) in refractory metastatic melanoma, starting at a dose level of 22 Gy, potentially associated with more toxicity from CONV and hence more difference between FLASH and CONV.

In conclusion, at the dose level of 15 Gy ultra-high and conventional dose rates had similar efficacy along with similar acute and late toxicity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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