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First in Human

Treatment of a first patient with FLASH-radiotherapy

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ABSTRACT

Background: When compared to conventional radiotherapy (RT) in pre-clinical studies, FLASH-RT was shown to reproducibly spare normal tissues, while preserving the anti-tumor activity. This marked increase of the differential effect between normal tissues and tumors prompted its clinical translation. In this context, we present here the treatment of a first patient with FLASH-RT.

Material & methods: A 75-year-old patient presented with a multiresistant CD30+ T-cell cutaneous lymphoma disseminated throughout the whole skin surface. Localized skin RT has been previously used over 110 times for various ulcerative and/or painful cutaneous lesions progressing despite systemic treatments. However, the tolerance of these RT was generally poor, and it was hypothesized that FLASH-RT could offer an equivalent tumor control probability, while being less toxic for the skin. This treatment was given to a 3.5-cm diameter skin tumor with a 5.6-MeV linac specifically designed for FLASH-RT. The prescribed dose to the PTV was 15 Gy, in 90 ms. Redundant dosimetric measurements were performed with GafChromic films and alanine, to check the consistency between the prescribed and the delivered doses.

Results: At 3 weeks, i.e. at the peak of the reactions, a grade 1 epithelitis (CTCAE v 5.0) along with a transient grade 1 oedema (CTCAE v5.0) in soft tissues surrounding the tumor were observed. Clinical examination was consistent with the optical coherence tomography showing no decrease of the thickness of the epidermis and no disruption at the basal membrane with limited increase of the vascularization. In parallel, the tumor response was rapid, complete, and durable with a short follow-up of 5 months. These observations, both on normal skin and on the tumor, were promising and prompt to further clinical evaluation of FLASH-RT.

Conclusion: This first FLASH-RT treatment was feasible and safe with a favorable outcome both on normal skin and the tumor.

Radiotherapy (RT) is an essential contributor for cancer cure but a substantial proportion of cancers are multi-resistant, especially to RT, defining an unmet clinical need for more effective and better tolerated forms of RT.

Delivering high curative radiation doses to tumors depends on the ability to spare normal tissues from the harmful effects of ionizing radiation. Over the last century, both fractionation [1] and precise volume optimization [2,3] appeared as the most powerful tools to increase both normal tissue tolerance and the differential effect between normal tissues and tumors. However, based on a strong pre-clinical rationale [4–13], FLASH-radiotherapy (FLASH-RT) is emerging as a third factor able to markedly improve the normal tissue tolerance, called the FLASH effect. This technology delivers the radiation dose almost instantaneously in milliseconds (ms) which is thought to induce a massive oxygen consumption and a transient protective hypoxia in normal tissue [8,14], as opposed to conventional RT delivering the same dose in minutes. In the tumors, which are generally hypoxic, the effect of FLASH-RT does not appear different from conventional RT [14]. In pre-clinical studies, FLASH-RT induced remarkably less side effects on healthy tissues, as compared to conventional dose rate RT, which in turn allowed to deliver higher doses to the tumor and improved tumor control [4,10,11]. The consistency of the phenomenon across tissues and species along with the magnitude of the differential effect

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observed in pre-clinical studies between tumors and normal tissues were very promising, and sustained its clinical translation [5,14].

However, since FLASH-RT has never been tested in patients, it was not possible to rule out possible over- or mis-interpretation (s) of the pre-clinical data that would lead to an unexpected adverse clinical outcome. In addition, FLASH-RT is by far more intense than conventional RT, using dose rates of several thousand times higher, and its protective effect on normal tissues might appear as "counterintuitive". In this context, we tested for the first time the effect of a FLASH-RT treatment in a patient.

Material and methods

Patient and tumor

A 75-year-old patient had a CD30+ T-cell cutaneous lymphoma diagnosed in 1999 classified T3 N0 M0 B0. He was initially treated with corticoids, PUVA-therapy (2001, 2004, 2006, 2007, 2008), Neostigason (2004, 2008), Caryolisin (2007), Methotrexate (2008, 2016–2017), Targretin 300 mg (2001, 2013, 2017), histone deacetylase inhibitor (Novartis LBH589; 2008, 2009), Caelyx (2011, 2012, 2013, 2014, 2017), brentuximab (2014–2015), resminostat (2017). None of these treatments could control the disease, which remained disseminated throughout the whole skin surface, although some non-durable responses could be observed (Supplement Fig. 1). In 2018, brentuximab was re-introduced but at a reduced dose (0.9 mg/kg) due to peripheral neuropathy limiting toxicity, together with prednisone (30 mg for 3 days) every 3 weeks.

Between 2008 and 2018, local skin RT has been extensively used for various progressive, ulcerative, and/or painful cutaneous lesions occurring despite the use of systemic treatments. RT was given either with KV X-rays, low energy electrons, or MV X-rays, depending on tumor sites and volumes. A total of 110 tumor sites (tumor size 1–5 cm) were treated, distributed on all parts of the skin surface. The most common regimens used were 20 Gy in 10 fractions, or 21 Gy in 6 fractions, which generally could control the lesions, given the radiosensitivity of this lymphoma. However, the tolerance of the skin was generally poor or very poor despite the relatively low RT total doses used, with typically high grade acute skin reactions that could take 3–4 months to heal for a lesion of 3–4 cm in diameter. This poor tolerance was attributed to a general skin frailty associated with the diffuse tumor infiltration and the multiple treatments received by the patient (Supplement Fig. 1). In this context, according to the pre-clinical data, FLASH-RT could offer an equivalent tumor control probability, while being less toxic for the skin.

Informed consent and administrative authorization

In June 2018, the patient was informed of the potential interest of FLASH-RT along with the fact that FLASH-RT had never been used in humans. He agreed to engage the administrative process for applying FLASH-RT on one of his most resistant and progressive skin lesions.

This treatment was performed in the frame of the Swiss federal medico-ethical directive described as "Distinction between standard therapies and experimental therapies in the individual context" approved by the Swiss Academy of Medical Sciences (ASSM) and transposed in our hospital under the N° DIM-DI-0112. The conformity of the FLASH treatment envisaged with this directive was verified by a committee of 3 experts, and included the cumulative conditions: (1) standard treatment hardly applicable; (2) Comparison unfavorable with the absence of treatment; (3) Disease progression carrying a risk for the patient; (4) expected side effects limited; and (5) Reasonable prospect of improvement.

After receiving a detailed information letter, the patient gave his consent for having one of the most symptomatic and progressive lesions treated by FLASH-RT, which was a 3.5-cm ulcero-infiltrating tumor situated on the right forearm (Fig. 1a). The treatment was approved by the Center of Experimental Therapies (CTE) of Lausanne university hospital and a review committee was created for follow-up, composed of two radiation oncologists, a medical oncologist, and a dermatologist. The treatment started after receiving the approval of the Swiss Federal Office of Public Health (OFSP).

Adaptation of the linac for clinical use

The FLASH-RT was performed using the Oriatron eRT6 5.6-MeV linac located at Lausanne University Hospital, and provided by PMB/Alcen (Peynier, France). This linac is a prototype specifically engineered for accelerating electrons in a FLASH mode. It has been used for pre-clinical irradiations, including treatments in cat-patients and pig, as previously described [11,15]. FLASH-RT consists in delivering a few pulses (generally $\leq$10), and in order to secure the treatment and prevent potential risks associated with this ultra-fast delivery, a stopping system able to monitor pulse by pulse was installed (PMB, France Peynier). This beam monitoring and stopping system (PMB part number P207100003) was based on the information of gun current and beam exit current to measure the number of pulses (fixed to 10), and beam-on time limitation 5% longer than the prescribed time (fixed for this patient to 95 ms since 10 pulses were delivered in an overall treatment time of 90 ms; see below).

Prescription of the dose and the dose rate

The prescription of the dose and dose rate took into account several parameters described below.

The first important parameter to consider was that the FLASH sparing effect of normal tissues has been essentially observed at high dose per fraction ($\geq$7–8 Gy), and shown to be remarkable at very high doses. Indeed, single doses as high as 34 Gy in a 2.6-cm field size and 31 Gy in 8-cm field size given to the skin of the pig could be tolerated with no or minimal acute and late effects [11]. Similar outcome was found for the skin/mucosa of cat-patients for whom up to 41-Gy single dose could be tolerated, and the maximal tolerated dose was not reached at this level [11].

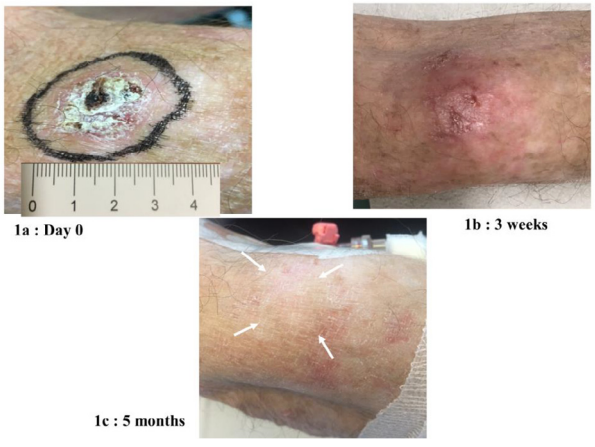

Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

Our patient had a long history of localized RT (110 different irradiations in about 10 years) and doses needed to control the lesions were typically 20–21 Gy in 6–10 fractions. Despite these relatively low total doses, the acute toxicity of these treatments was found to be relatively severe in the context of the particular skin frailty of this patient, with commonly 3–4 months for complete healing. Taking this into account, a dose of 15 Gy was proposed, high enough to trigger a FLASH effect and likely sufficient for obtaining a tumor control in this particular lymphoma. As extrapolated from our pre-clinical studies, the hypothesis was that the "equivalent FLASH dose for normal tissues" would be about 2/3 of the prescribed dose, i.e. around 10 Gy and the "equivalent-FLASH dose for the tumor" would be the real prescribed dose of 15 Gy [11,14]. Following this hypothesis, a single dose of "10-Gy-equivalent for normal tissues" was considered as feasible for this patient, although being likely at the upper acceptable limit given the previous history of severe acute skin reactions with fractionated 20–21 Gy.

The second key aspect in order to reproduce a FLASH effect in human normal tissues, was to use the parameters that were strongly correlated with a FLASH effect in pre-clinical studies *in vivo*. These data showed that the most relevant parameters were the combination of dose in the pulse ($\geq$1.5 Gy), dose-rate within the pulse ($\geq 10^6$ Gy), and overall irradiation time (<200 ms, but preferably less) [14]. Taking these considerations into account, the dose of 15 Gy was given in 10 pulses each of 1 μs, with a repetition rate of 100 Hz, which led to an overall treatment time of 90 ms. A 5-mm bolus was added so that the total depth covered by the 90% isodose was 1.3 cm, taking into account the thickness of the tumor.

Treatment set-up and RT-quality assurance

The treatment set-up is to be found in Supplement Fig. 2. Redundant dosimetric checks were performed before, after, and during the treatment. This general dosimetric approach was transposed from the one previously used for pre-clinical experiments [15–17].

Before and after the treatment, GafChromic films measured dose profiles and alanine pellets the absolute dose at the center of the beam. The percent depth dose (PDD) of the treatment configuration was compared with the PDD obtained during the commissioning and showed with the 5-mm bolus an increase of the skin surface dose from 90% to about 100% while the R_{50} index was not modified (supplement Fig. 3a). Pre-irradiation dose profile measurements confirmed the defined field size and the homogeneity (Supplement Fig. 3b). The average doses measured with alanine pre- and post-irradiation were 15 and 14.8 Gy, respectively, in agreement with the prescribed dose. The corresponding pre- and post-irradiation dose distributions measured with GafChromic films are shown in supplement Fig. 3c. The absolute doses measured with the films at the center of the beam were 15.1 and 14.8 Gy, respectively.

These dosimetric checks performed before and after the treatment in conditions mimicking the treatment were completed during the treatment by using alanine pellets positioned at the limit of the PTV under the 5-mm bolus (Supplement Fig. 2b). Doses of 14.6 and 13.7 Gy were recorded for pellet A and B, respectively (Supplement Fig. 2c). Given that the pellet A was placed in the 98% isodose and the pellet B was in the 92% isodose (according to measures shown in supplement Fig. 3), the prescription point received a dose of 14.9 Gy (±0.3 Gy, SD) and the PTV coverage was at least 95% of the prescribed dose.

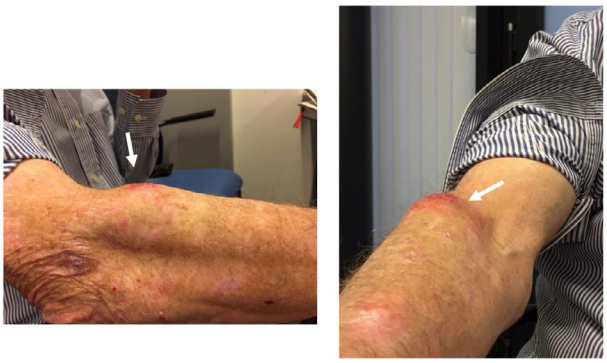

Fig. 2. Appearance in soft tissues surrounding the tumor of a transient non symptomatic edema, grade 1 NCI-CTCAE v 5.0 (maximal at day 15).

Results

A tumor of 3.5 cm (Fig. 1a) was treated with 15 Gy in 90 ms. The patient reported to have observed a "blue flash" issued from the linac during the treatment, likely due to the Cherenkov light emitted by the electron beam in tubular PMMA applicator. This "flash" was also recorded on a camera. After the treatment, a follow-up was performed on a twice weekly basis and on a weekly basis after one month.

A redness was observed on the skin surrounding the tumor between day 10 and 44, with a maximal reaction at 3 weeks consisting of asymptomatic mild epithelitis (grade 1 according to NCI-CTCAE v 5.0, Fig. 1b). Between days 12 and 24, a grade 1 edema (NCI-CTCAE v 5.0) was observed, situated under the skin, surrounding the tumor (Fig. 2). Such an edema was never observed after his 110 previous irradiations, including those performed under the same systemic treatments (corticoids and brentuximab). The timing was concomitant with the disappearance of the tumor. No biopsy was taken since this edema was not symptomatic, and a biopsy has not been planned in the inform consent.

As shown in Fig. 3, the irradiated skin appearance in the PTV around the tumor (GTV) was evaluated by optical coherence tomography examination, and compared to the normal non-irradiated skin. At 3 weeks, i.e. at the peak of the skin reactions (grade 1, Fig. 1b), there was no decrease of the thickness of the epidermis and no disruption at the junction dermis/epidermis along with hair follicles loss and some limited increase of the vascularization, all consistent with the clinical examination.

The tumor started to shrink around 10 days after irradiation with a complete tumor response at 36 days which was durable for the subsequent 5 months (Fig. 1c).

Discussion

Several pre-clinical studies and a clinical veterinarian study showed a major sparing effect of FLASH-RT on normal tissues as compared to conventional RT, while preserving the same effect on tumors [4,6–13]. These outstanding observations justified its clinical translation, offering a new opportunity to improve radiation and cancer treatments [5,14].

It is not possible to draw any firm conclusion from this report about the relative importance of a FLASH effect in human tissues, given the historical and indirect nature of the comparison with conventional RT, along with potential confounding factors such as the exposure to concomitant treatments. However, some important conclusions can be drawn from this first FLASH treatment. Indeed, this experience showed the technical feasibility and clinical safety of delivering a high single FLASH dose in a patient. The overall treatment time of 90 ms proved to be feasible, and the dose measured was very similar to the prescribed dose.

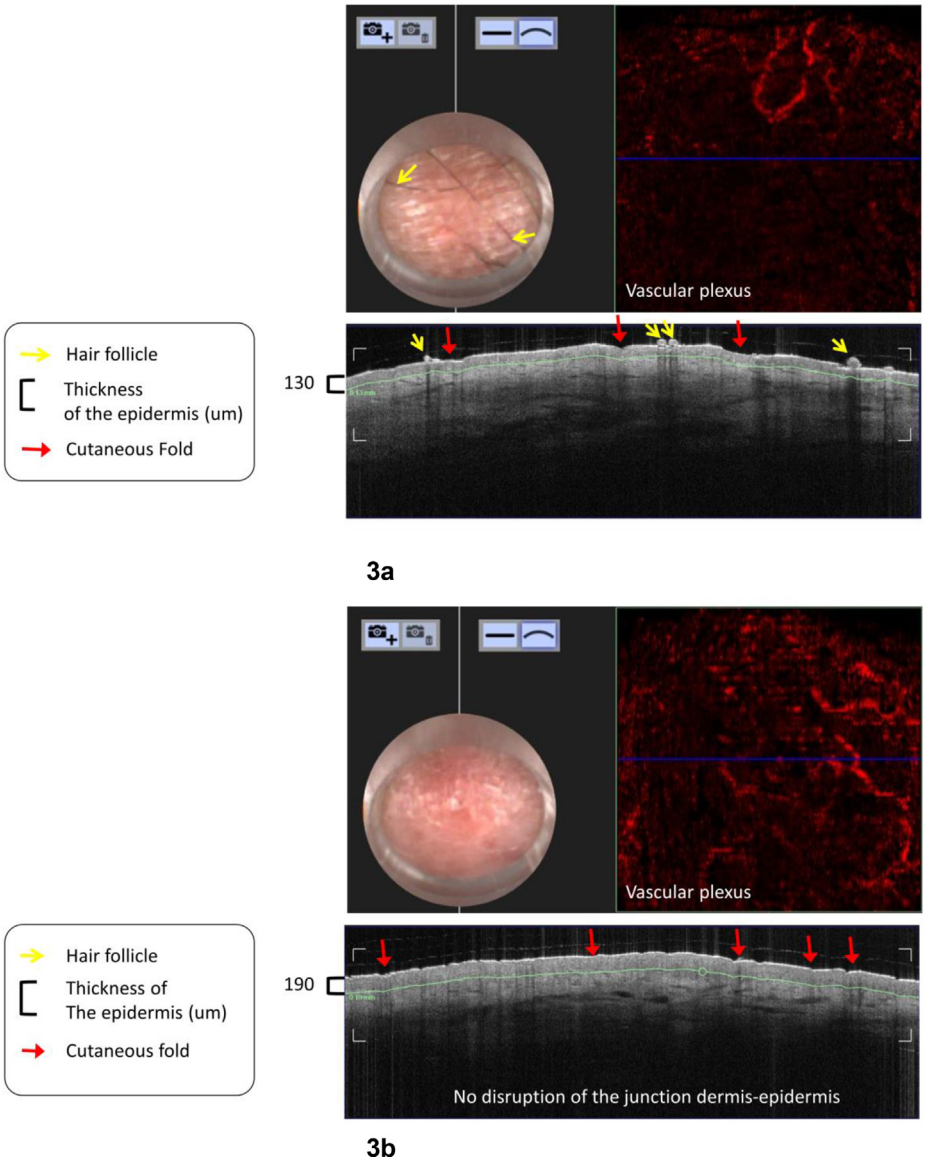

Fig. 3. Appearance of the skin with optical coherence tomography. Comparison between normal skin (a) and the irradiated skin in the PTV around the tumor (b), at the peak of reactions (3 weeks). The irradiated skin appeared with a slight increase of the thickness of the epidermis and without any disruption of the basal membrane. Some degree of hyperthemia was noted as well as hair loss. All these observations were consistent with the clinical observations.

The skin reactions did not exceed grade 1, but even in conventional delivery, one would expect that a higher dose in a single fraction should be needed to produce high grade toxicity [18]. However for this particular patient, when compared to previous skin reactions after exposure to 20 Gy in 10 fractions (Biological Equivalent Dose for alpha/beta 10, BED_{10} = 24 Gy) or 21 Gy in 6 fractions (BED_{10} = 28.35 Gy), the FLASH-RT reactions associated with this 15 Gy single dose (BED_{10} = 37.5 Gy) were minimal and disappeared in a much shorter time. In parallel, the tumor response appeared rapid, complete, and durable with a short follow-up of 6 months. These observations, both on normal skin and on the tumor, were compatible with a FLASH effect, and do not suggest any unexpected outcome that would preclude further clinical evaluation of FLASH-RT.

The transient edema observed in soft tissues surrounding the tumor was intriguing since it has never been observed after the numerous previous irradiations that the patient underwent. This could be interpreted as a direct toxic effect of the irradiation; however, this is hardly compatible with the rapid dose decrease in tissue associated with low energy electrons, and also hardly compatible with the relatively minimal epidermis reactions, where the highest dose was received (Figs. 1b and 3). Alternatively, it might be related to a tumor-related inflammatory/immune response induced by the irradiation [19]. In fact, there are several characteristics of FLASH-RT as compared to conventional RT that could lead to differences of the immune response. Indeed, FLASH-RT best operates at high dose per fraction, and this could be associated with massive tumor antigens release [19]. In addition, the "general" protective effect of FLASH could apply to all types of normal cells including immune cells, while the instantaneous nature of the irradiation could spare the circulating lymphocytes by minimizing their exposure to ionizing radiation, as shown previously with a proportion of undamaged lymphocytes that could increase with the dose rate [20]. Moreover, the immune cells attacked into the tumor by the radiation-induced inflammation cannot be destroyed by subsequent repeated fractionated irradiation dose(s), as opposed to conventional RT. This may suggest for future clinical studies to carefully explore and monitor potential

correlations between the FLASH-RT effect and the immune response.

In conclusion, this first FLASH-RT treatment was feasible and safe, and its favorable outcome both on normal skin and the tumor supports its further clinical evaluation.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.019.

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