Unexpected healing of radiation-induced scalp lesions with OTR4120, a heparan sulfate mimetic

An 80-year-old woman presented to us with two painful scalp lesions. The patient had a medical history of multiple basal cell carcinomas following Grenz ray radiation therapy in 1946 for seborrhoeic eczema on her scalp. The patient was diagnosed with two nodular basal cell carcinomas on the scalp. After excisions and full thickness transplantations, partial necrosis developed in the transplanted skin covering the lesions. Thereafter, two ulcers developed, both exposing the scalp bone.

Ulcerative lesions, a known complication of radiation therapy, are reported to be caused by the poor vascular and healing capacity of irradiated skin. Patients suffering from radiation-induced scalp lesions are often therapy resistant [1, 2].

Our patient had been treated for several months with a variety of wound dressings [3], with no sign of granulation at the wound edges or the base of the ulceration. Therefore, we chose a novel way of potentiating the tissue's ability to regenerate by the use of heparan sulfate (HS) mimetic OTR4120 [4]. Before starting this treatment (when the ulcers had been present for over 4 months), the larger wound measured 2.3×1.5 cm *(figure 1A)* and the smaller wound 1×0.5 cm. A gauze soaked with OTR4120 was applied for 10 minutes, twice weekly for 8 weeks,

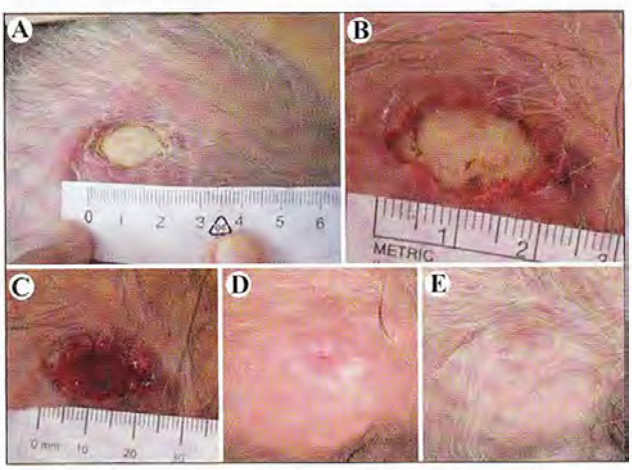

Figure 1. Radiation-induced scalp lesions in a woman known with multiple basal cell carcinomas later healed with heparan sulfate mimetic OTR4120. **A)** Largest ulcer before treatment with a heparan sulfate mimetic OTR4120. **B)** Granulation tissue formation, after 4 weeks of treatment. **C)** Lesion completely covered with granulation tissue after 6 weeks of treatment. **D)** Lesion completely covered at week 12. **E)** No recurrence of ulcer at week 24.

on the debrided wound. After 2 weeks the wound status markedly improved: granulation tissue formed at the wound edges. Over time the process of wound healing progressed *(figure 1B, C)*. Noticeably, after one month, the patient's wellbeing improved and she reported the absence of pain. During treatment weeks 2 to 8, vital granulation tissue grew from the wound edges over the dry bony structure until granulation tissue completely covered the ulcer. Treatment was ceased at week 8 when granulation tissue entirely covered the wounds. At this time the wounds measured 1.5×0.8 cm and 0.2×0.2 cm; hereafter, we applied only inert wound dressings until the wounds were closed at week 12 *(figure 1D)*. When the patient returned to our unit 24 weeks after start of treatment, the ulcers had remained completely healed *(figure 1E)*.

In healthy tissue, the extracellular matrix (ECM) consists of a network of scaffold proteins that are bridged by sugar-based polymers, called glycosaminoglycans, of which HS is a prominent example. HS is not only a structural element of tissue architecture, but is also a storage and protection site of a large variety of locally synthesized HS-bound polypeptides. These include chemokines, angiogenic factors, morphogens, and GFs. In this way, HS regulates the bioavailability of these signals and maintains the delicate balance between tissue integrity and tissue disruption, allowing the cellular tissue components to unfold their natural mechanism to achieve tissue homeostasis. However, in an acute wound healing process, inflammatory cells activate the production of glycanases and proteases that destroy the ECM, including HS. Through this degradation, the orchestrating role of HS in GF sequestration is lost [5].

In wound tissue, protease and glycanase-resistant OTR4120 can replace the degraded HS and bind to the free HS-binding sites that become available following HS degradation. The affinity constant of OTR4120 toward matrix proteins allows a tight binding. This makes a short term exposure to OTR4120 sufficient. Once OTR4120 is in place in the matrix scaffold, the growth signaling peptides can be positioned through OTR4120 binding in this restored micro-environment. In this way, OTR4120 is thought to offer a matrix therapy that restores the natural cellular microenvironment and the endogenous signaling of cell communications needed for tissue regeneration, thereby halting the self-perpetuating cycles, particularly in impaired healing wounds [6].

This patient with treatment-resistant scalp ulcers derived benefit from this OTR4120 treatment, which might also be used for other hard-to-heal skin wounds of arterial, venous or diabetic origin. ■

Disclosure. *Conflict of interest: Medical device OTR4120 (trade name Cacipliq20) was provided free of charge by its manufacturer OTR3, Paris, France.*

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