Photodynamic Priming Affects the Radiation-Induced Skin Toxicity and Damage Timeline

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Introduction

Photodynamic therapy using 5-aminolevulinic acid (ALA-PDT) generates intracellular protoporphyrin IX (PpIX), which upon light activation produces reactive oxygen species and triggers vascular and metabolic modulation. At low, non-ablative doses, PDT does not induce cytotoxicity but can transiently increase blood flow, oxygenation, and local inflammation—an approach referred to as photodynamic priming.

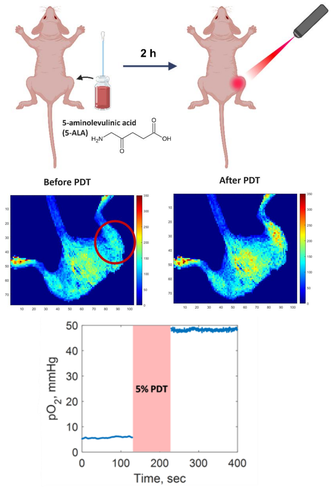

Figure 1: A schematic depiction of ALA-PDT (top); Increase in blood volume (middle) and; in tissue oxygenation following low sub-therapeutic dose of PDT (bottom)

PDT increases perfusion and oxygenation and may alter the timing and severity of radiation-induced skin injury.
This study investigates how sub-therapeutic ALA-PDT priming affects (1) early skin toxicity, (2) structural skin changes, and (3) histological remodeling after CDR and UHDR irradiation.

Methods and Materials

Delivery parametres:

- IntraOp Mobetron 9 MeV Electrons
- UHDR: 340 Gy/s, 3 Gy per pulse, 90Hz
- CDR: 0.16 Gy/s

Irradiation setup:

- C57Bl/6 female mice, 10-12 weeks old
- Immobilized via 3D printed Jig
- Dose groups: 24 Gy, 27 Gy

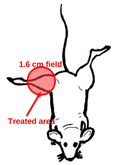

Figure 2: A depiction of the irradiation field positioning

Data collection:

- 30-day follow-up with clinical skin scoring
- Histology (H&E) at 10 days post-RT
- Optical Coherence Tomography (OCT) imaging of epidermal thickness and edema (Days 1–14)
- OCT structural assessment for ulceration and architectural loss

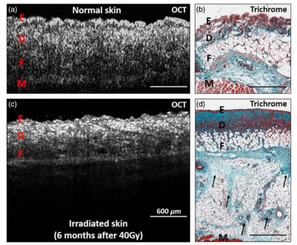

Fig. 5 OCT structural images and Masson's trichrome stains of (a, b) normal and (c, d) irradiated mouse skin. Tissue layers are labeled with E, epidermis; D, dermis; F, fat; and M, muscle. (a, c) Structural OCT imaging shows thinning of epidermal layer, changes in dermal thickness, and modification of microrelief of the skin surface in irradiated skin. In accord with *in-vivo* OCT, (b, d) trichrome histologic staining shows similar trends in skin layer changes and a further increase in collagen deposition [indicated with black arrows on (d)] after irradiation stemming from parenchymal damage to soft tissue. Radiation-induced increase in dermal thickness and reflectivity limits OCT penetration to the deeper muscle layer [appearing red at the bottom of the trichrome image in (d)]. Scale bars are 0.6 mm.

Figure 3: An example of the OCT scan of the mouse skin compared to the histological staining demonstrating its capacity to visualise the different layers of the skin

We plan to study the microscopical changes in the skin following regular RT and ALA-PDT RT to establish the mechanism behind the priming of the tissue

Results

- PDT priming resulted in the immediate increase of radiation damage as early as day 1 post-RT as shown in Figure 4
- Both dose levels demonstrate the enhanced radiation and PDT damage in the early acute stage of the radiation damage curve
- We observed a change in the late acute effects as well – both dose and dose rate cohorts of mice are demonstrating the skin healing following photodynamic priming

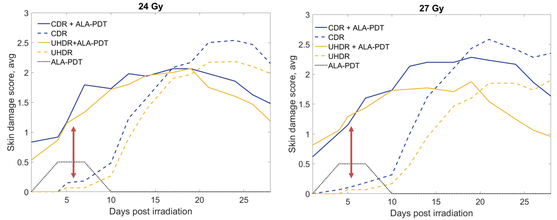

Figure 4: Comparison of the radiation-induced toxicity between primed and non-primed cohorts. The arrows point out the difference in the amount of damage the mice receive in the early (before day 10) stage. A dotted line represents the control cohort of mice only receiving 5 J/cm² ALA-PDT treatment

SCORE	DESCRIPTION OF SKIN RESPONSE OBSERVED AT EACH LEVEL
0.0	Normal skin
0.5	50/50 chance if there is any difference from normal
0.75	Definite but slight abnormality
1.0	Definite abnormality with reddening
1.25	Severe reddening and/or white scales and/or puffiness
1.5	Moist breakdown in one very small area, with scaly or crusty appearance
1.75	Moist desquamation in small areas (more definite than 1.5)
2.0	Breakdown in large area, possibly moist in places
2.5	Breakdown in large areas of skin with definite moist exudate
3.0	Breakdown in most of skin with moist exudate
3.5	Complete moist breakdown of limb—often stuck to body

Table 1: Visual Scoring system for acute skin damage in mice.

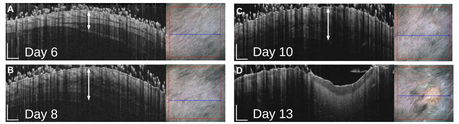

Figure 5. Timeline covering the span of 6-13 days post-RT for a mouse receiving 24 Gy CDR

- The main difference lies in the early acute stage following the irradiation – often before the visual irradiation damage takes place
- Techniques like OCT and computational pathology offer insight into the microscopical changes that take place before the macroscopical changes take place
- Figure 5 offers an example of the early damage markers like hyperdermal edema that is noticeable as early as day 8 post-Rt, while the ulceration takes place on day 13
- Figure 6 demonstrates that the inflammation (number of the infiltrating cells per 90x80 μm ROI) also increases after 10 days after irradiation
- Taken together these metrics will provide a necessary insight into the mechanism behind the difference in the damage timeline of the photodynamic priming

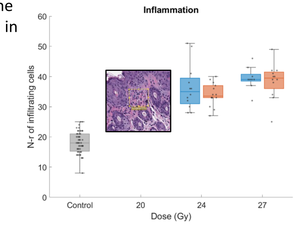

Figure 6. Comparison of the inflammation markers 10 days post-RT, demonstrating the increase in the number of infiltrating cells before the visual damage takes place

Conclusions

Low-dose ALA-PDT priming substantially alters the temporal trajectory of radiation skin injury. The markedly earlier onset of damage (Day 4–5) suggests that priming modifies vascular or metabolic conditions that sensitize the skin to radiation.
The similarity in response acceleration for both CDR and UHDR indicates that priming affects radiation-independent pathways such as perfusion, inflammation, oxidative stress, or epithelial turnover.
The combination of clinical scoring, OCT structural imaging, thickness quantification, and multi-timepoint histology will provide a comprehensive framework for understanding how microenvironmental perturbation modifies RT toxicity.

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