

MINI-REVIEW

Granulocyte colony-stimulating factor in radiation dermatitis: A mini-review of the rationale and current evidence

Saarthak Miglani¹, Faiz Akram Ansari, Tanshi Daljit¹, and Sapna Yadav

Department of Radiation Oncology, Maulana Azad Medical College, Delhi, India

Abstract

Radiation dermatitis represents one of the most prevalent sequelae of external beam radiotherapy. It has been attributed to epithelial stem cell depletion, microvascular injury, and dysregulated inflammatory signaling. Granulocyte colony-stimulating factor (G-CSF), conventionally employed for hematologic support to treat chemotherapy-associated neutropenia, is increasingly being recognized as a pleiotropic cytokine with regenerative, angiogenic, and immunomodulatory properties, supporting its potential use in the management of radiation dermatitis. Over the past decade, conceptually compelling, though limited, clinical evidence has emerged suggesting that localized administration of G-CSF may accelerate re-epithelialization, preserve treatment continuity, and improve patient-reported outcomes in radiation dermatitis. This review integrates contemporary insights into cutaneous radiobiology with emerging translational and clinical data on G-CSF, underscoring it as a potential regenerative adjunct in supportive radiation oncology.

***Corresponding author:**
Tanshi Daljit
(tanshidaljtit@gmail.com)

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1. Introduction

Radiation dermatitis (RD) is a universal accompaniment of external beam radiotherapy, with reported incidence exceeding 90% among head & neck, breast, thoracic, and pelvic malignancies.¹ While early erythema and dry desquamation are seen in about 80% of these patients, a clinically meaningful subset of patients (~15%) progress to severe reactions such as moist desquamation and ulceration,^{2,3} posing a major hurdle in continuation of radiotherapy as well as negatively impacting the quality of life.

Radiation dermatitis is a part of the broader spectrum of epithelial toxicities encountered in oncology, including treatment-related cutaneous reactions and mucositis across radiotherapy, chemotherapy, and targeted therapies. Recent comprehensive reviews have emphasized shared biological mechanisms such as epithelial stem cell depletion, inflammatory dysregulation, and microvascular injuries across these entities.⁴ Clinically, high-grade RD is associated with pain, functional impairment, risk of secondary infection, psychological distress, and, most importantly, unplanned treatment interruptions. Prolongation of overall treatment time has been repeatedly correlated with inferior tumor control in rapidly proliferating malignancies—an indirect consequence of

severe skin toxicity associated with radiotherapy.^{5,6} Despite its prevalence and clinical relevance, the management of RD remains largely empirical, anchored in topical corticosteroids, emollients, and dressings with modest and inconsistent efficacy.⁷

This therapeutic stagnation has prompted renewed interest in biologically driven strategies that address the fundamental failure of tissue regeneration underlying RD. Within this context, granulocyte colony-stimulating factor (G-CSF) has emerged as a potential therapeutic strategy. The current review specifically focuses on radiation-induced cutaneous injury while exploring the mechanistic rationale and emerging clinical evidence for G-CSF in this defined setting.

2. Pathophysiology: Failed tissue regeneration and vascular injury

Under normal circumstances, skin homeostasis is maintained by actively dividing cells in the basal layer of epidermis. Ionizing radiation depletes this basal cell layer and impairs re-population of the damaged areas of the epidermis. This process is accompanied by altered keratinocyte expression, with a shift from high-molecular-weight keratins 1 and 10 to lower-molecular-weight keratins 5 and 14,⁸ together with reduced levels of transforming growth factor- β , vascular endothelial growth factor, hepatocyte growth factor, and fibroblast growth factor.⁹

Concurrently, radiation inflicts damage on dermal endothelial cells, resulting in capillary rarefaction, impaired perfusion, and tissue hypoxia. These vascular alterations are now recognized as the quintessential determinants for delayed healing and chronic radiation injury.¹⁰ The

persistent activation of inflammatory and profibrotic cytokine networks further disrupts the finely regulated sequence of inflammation, proliferation, and remodeling required for effective wound repair.¹¹

These events together result in breakdown of the epidermal barrier, moist desquamation, and eventual ulceration, without timely intervention.

3. Granulocyte colony-stimulating factor: A cytokine wonder

Although traditionally regarded as a lineage-specific hematopoietic growth factor, G-CSF is increasingly recognized as a pleiotropic cytokine with substantial roles in tissue repair and regeneration (Table 1).

3.1. Progenitor cell mobilization

Granulocyte colony-stimulating factor is a potent mobilizer of bone marrow-derived progenitor cells, including endothelial progenitor cells, which home to sites of tissue injury and participate in vascular regeneration and stromal repair.¹² Endothelial progenitor cell mobilization is particularly relevant in irradiated skin, where microvascular injury represents a critical step in healing.

3.2. Angiogenesis and microvascular restoration

Preclinical studies demonstrate the role of G-CSF in enhancing angiogenesis through upregulation of vascular endothelial growth factor and stimulation of endothelial cell proliferation and migration.¹³ Restoration of microvascular integrity improves tissue oxygenation and establishes a permissive environment for re-epithelialization in radiation-afflicted skin.

Table 1. Biological rationale of granulocyte colony-stimulating factor (G-CSF) in radiation dermatitis (RD)

Pathophysiological component of RD	Effect of radiation	Proposed role of G-CSF	Supporting evidence type
Basal cell depletion	Impaired re-epithelialization	Stimulates keratinocyte migration	Preclinical
Microvascular injury	Capillary rarefaction, hypoxia	Endothelial cell proliferation and angiogenesis	Animal studies
Inflammatory dysregulation	Persistent cytokine activation	Immunomodulation	Mechanistic studies
Delayed wound healing	Impaired remodeling	Growth factor signaling	Translational data

Note: Synthesized from Refs. ¹²⁻¹⁵

3.3. Immunomodulation and resolution of inflammation

Beyond neutrophil expansion, G-CSF exerts nuanced immunomodulatory effects, influencing macrophage and dendritic cell polarization towards a reparative phenotype and facilitating resolution of inflammation.¹⁴ Given that persistent inflammatory signaling perpetuates tissue injury in RD, this immunoregulatory function could potentially counter the injury cascades.

3.4. Effects on keratinocyte dynamics

Barrientos *et al.*¹⁵ demonstrated that colony-stimulating factors influence keratinocyte migration and proliferation and thus support epithelial closure during wound repair. These observations provide a plausible mechanistic link between G-CSF administration locally and accelerated re-epithelialization.

3.5. Effect of peri-lesional infiltration of granulocyte colony-stimulating factor in the background of compromised vasculature

Radiation dermatitis is characterized by microvascular rarefaction rather than complete vascular obliteration, and thus, residual capillary networks at the wound periphery remain functionally active.¹³ The high interstitial concentration of G-CSF achieved by localized infiltration directly upregulates endothelial growth factors, leading to angiogenesis and indirectly stimulates keratinocytes, macrophages, and the fibroblasts in the vicinity to initiate and sustain the reparative cascade.^{13,14}

4. Clinical evidence for granulocyte colony-stimulating factor in radiation dermatitis

The first clinical exploration of G-CSF in RD was undertaken by Viswanath *et al.*¹⁶, wherein patients with grade III radiation-induced moist desquamation received a single dose of G-CSF 300 µg subcutaneously at the periphery of the wound. Time to healing was defined as the number of days from local G-CSF administration to complete healing/re-epithelialization of the open wound. The mean duration of resolution of moist desquamation was 6.6 ± 4.7 days. Overall, 56.5% patients reported a rapid reduction in the severity of their grade III reactions and were able to resume their treatments within five days. Furthermore, 86% of patients achieved wound healing within 10 days, which was substantially faster than the anticipated 2 to 3 weeks for reactions of this severity. Despite limitations related to sample size and the absence of a comparator arm, the study was conceptually important in establishing feasibility and identifying a biologically meaningful signal of G-CSF activity in RD.

Further definitive evidence emerged from a phase II trial by Das *et al.*¹⁷ in 2023. They recruited 122 patients with grade III/IV skin reactions from radiotherapy of various subsites and randomized them into two arms; the control arm ($n = 60$) received standard topical & oral steroids with antibiotics along with topical gentian blue, whereas the experimental arm ($n = 62$) received G-CSF infiltration around the region of desquamation and ulceration in addition to topical and oral treatments. The mean duration of re-epithelialization was reported to be 5.2 days in the experimental arm and 7.5 days in the control arm, suggesting a statistically significant gain of two days (at minimum) in healing by G-CSF administration. Additionally, the proportion of patients experiencing treatment gaps was lower in the experimental arm by about 20%. The mean duration of treatment interruption was also shorter in the experimental arm (3.1 vs. 4.9 days). They also reported a grade-adjusted hazard ratio of non-resolution of toxicity for the control arm to be 2.98 ($p = 0.046$). Thus, G-CSF resulted in significantly faster epithelial recovery, fewer treatment interruptions, and improved patient-reported quality-of-life outcomes. Localized administration was well tolerated without any significant adverse events. The main limitations were its single-institution design and the inability to compare different administration routes and dosing protocols. Important findings from both the studies described above are summarized in Table 2.

Evidence from studies on radiation-induced mucositis and chronic wound healing with G-CSF provides indirect support for epithelial repair mechanisms, suggesting potential translational relevance to cutaneous epithelial repair.^{18,19}

5. Safety and oncologic considerations

Administration of G-CSF is associated with several acute adverse effects, most commonly generalized musculoskeletal pain, affecting approximately 20 to 25% of patients. Other common effects include headache, fatigue, and nausea.²⁰ These reactions were reported in less than 10% of patients in studies by Das *et al.*¹⁷ & Viswanath *et al.*¹⁶, and all of them were self-limiting. None of the patients reported exacerbation of radiation toxicities. Long-term safety data remain limited. Concerns regarding secondary malignancies have mainly been reported in the context of routine prophylactic G-CSF use with chemotherapy to prevent/treat neutropenia²¹, and their relevance to single-session local infiltration for RD remains uncertain.

6. Knowledge gaps and future directions

Despite promising and biologically plausible signals, the evidence base remains hypothesis-generating and is

Table 2. Clinical evidence of granulocyte colony-stimulating factor (G-CSF) in radiation dermatitis (RD)

Study	Year	Design	No. of Patients	Grade of RD included	Intervention	Comparator arm	Key outcomes	Limitations
Viswanath <i>et al.</i> ¹⁶	2012	Prospective pilot	23	III	Single dose of 300 mcg perilesional G-CSF	None	(i) 86% patients demonstrated healing of their wounds within 10 days	No control arm; small sample size
							(ii) Mean duration to resolution of moist desquamation was 6.6 ± 4.7 days	
							(iii) The location of the lesion and the depth of skin reaction significantly affected the rate of skin healing	
Das <i>et al.</i> ¹⁷	2023	Randomized phase II	122	III & IV	Intradermal G-CSF + standard of care (topical & oral steroids with antibiotics along with topical gentian blue)	Standard of Care	(i) The mean duration of re-epithelialization shorter in the G-CSF arm (5.2 vs. 7.5 days)	Single center
							(i) Mean duration of treatment break also reduced to 3.1 days (vs. 4.9 days) in the G-CSF arm	
							(i) Grade-adjusted hazard ratio of non-resolution of toxicity for the control arm = 2.98 ($p = 0.046$)	

insufficient to support routine incorporation of G-CSF infiltration into clinical practice for managing RD. Available data are derived from small pilot studies and a single phase II trial, with heterogeneity in patient populations, dosing schedules, routes of administration, and clinical endpoints. The absence of large, multicenter randomized controlled trials limits generalizability and precludes definitive recommendations. Key unresolved issues include optimal dose, timing, and frequency of administration, as well as the relative merits of prophylactic versus therapeutic use. Furthermore, patient selection criteria remain undefined. Interaction with modern radiotherapy techniques and concurrent systemic therapies has not been systematically explored either. Incorporation of biomarker-driven and tissue-based correlative studies is also required to validate angiogenic, immunomodulatory, and regenerative effects of G-CSF *in vivo*. In addition, long-term safety requires formal evaluation.

7. Conclusion

Radiation dermatitis is a common toxicity of radiotherapy that is driven, in part, by impaired tissue regeneration and vascular injury. G-CSF, traditionally used for hematologic support, possesses a constellation of biological effects that closely align with the pathophysiology of radiation-induced skin injury. Contemporary clinical evidence, though limited, suggests that localized G-CSF administration may accelerate healing, preserve treatment continuity, and improve patient experiences. Reframing G-CSF as a regenerative adjunct opens a promising and underexplored avenue in supportive radiation oncology.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Saarthak Miglani

Writing – original draft: Saarthak Miglani, Tanshi Daljit

Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

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