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Commentary

Early clinical signals for Placental Mesenchymal Stem Cell Hydrogel in Radiation-induced Skin Injury

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ABSTRACT

Background: Radiation-induced skin injury (RSI) affects 85-90% of radiotherapy patients, with limited effective treatment options available. A recent Phase II randomized controlled trial investigated the efficacy of placental mesenchymal stem cell (PMSC)-embedded alginate hydrogel for treating moderate-to-severe RSI.
Methods: This commentary analyzes the double-blinded, placebo-controlled trial by Tian et al. (N= 66), which evaluated once-daily PMSC hydrogel application (1×10^6 viable PMSCs) for six days in patients with grade II or higher RSI. Primary endpoints included overall recovery rate, wound regression, and dermatitis severity scores.
Results: The PMSC hydrogel group demonstrated statistically significant improvement in healing rates ($p < 0.001$), with 64% relative risk reduction in wound progression compared to placebo. Radiation-Induced Skin Reaction Assessment Scale scores and pain relief showed significant benefits by Day 6. TGF-β1 biomarker elevation suggested native tissue repair mechanisms. No serious adverse events were reported during the study period. Key constraints include a single-center design, a small sample size, a 15-day follow-up duration, the absence of quality-of-life improvements on the EORTC QLQ-C30, and the lack of reported cancer types or radiation regimen details, limiting generalizability.
Conclusion: The trial presents encouraging preliminary evidence supporting PMSC hydrogel's potential in accelerating the RSI healing process. However, definitive conclusions regarding practice-change efficacy require confirmation through larger, multicenter Phase III trials with extended follow-up (3-6 months), comprehensive patient-centered outcomes, cost-effectiveness analysis, and through assessment of late effects, including fibrosis.

1. Context

The recent Phase II randomized controlled trial by Tian et al. [1] reporting the efficacy of a placental mesenchymal stem cell (PMSC)-embedded alginate hydrogel in the treatment of radiation-induced skin injury (RSI) represents a compelling signal in oncology supportive care and regenerative medicine. RSI is a common quality-of-life-limiting complication, with acute radiation-induced dermatitis having been noted to occur in a high proportion of patients (most cited as 85–95%, varying by anatomical site and treatment group) [2, 3]. While evidence-based suggestions have been given to employ mild cleansing, topical steroids, and other interventions, no single treatment has demonstrated consistently superior efficacy across diverse patient populations and radiation regimens [2, 3].

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2. Key Findings from Tian et al.

Tian et al. performed a double-blind, randomized, placebo-controlled trial (N=66) in a single-center trial [1]. The inclusion criteria of this trial comprised patients with Cancer grade II or higher RSI according to RTOG/EORTC criteria, including male (n=23) and female (n=43) patients with an average RSI lesion area of 779 mm² [1]. The location of RSI was on the neck, limbs, chest, axilla, perineum, or groin [1]. The patients were randomly allocated in a 2:1 ratio to groups receiving PMSC Hydrogel (N=44) or placebo (N=22) [1].

The PMSC hydrogel contained 1×10^6 viable PMSCs, with a sodium alginate matrix (1.2 g, which covered an area of 15 cm^2), which was applied once a day for a period of six days [1]. The controls received a placebo gel of similar appearance, devoid of cellular matter [1]. Follow-up was continued until Day 15 [1].

The primary endpoint of the overall recovery rate showed encouraging phase II results. The treatment group showed a statistically significant improvement in healing rate from Day 1 through Day 6 relative to placebo ($p<0.001$ overall trend). Moreover, the PMSC hydrogel showed significant benefit in inhibiting the increase in the wound size from Day 2 onward ($p<0.05$ from Days 2–6), with only 18% (8/44) patients in the treatment group fulfilling the measure of

increased wound area relative to 50% (11/22) patients in the control group, reflecting an estimated 64% relative risk reduction.

The Radiation-Induced Skin Reaction Assessment Scale (RISRAS) scores showed a significant improvement in the treatment group compared with controls on Day 6 (p=0.001). Pain relief measured on the Numeric Rating Scale (NRS) revealed greater relief in the PMSC gel group versus placebo by Day 6 (between-group difference p=0.0399) [1]. Although the original trial presented these data graphically showing trends toward reduced pain scores, the clinical significance relative to established minimal clinically important difference (MCID) thresholds (typically 1.3-2.0 points for NRS in pain studies) was not explicitly addressed [1].

Among biomarkers evaluated, TGF-β1 levels increased significantly in the treatment group (p=0.05) [1]. This represents an exploratory biomarker signal consistent with tissue repair pathways; however, TGF-β1's pleiotropic roles (promoting both healing and fibrosis) necessitate longer follow-up to monitor for potential pro-fibrotic effects [4]. The timing and methodology of TGF-β1 measurement (whether from serum, wound fluid, or tissue) and its correlation with clinical outcomes were not fully detailed in the trial report [1].

The treatment was well-tolerated with no serious adverse events reported during the study period [1]. However, the six-day treatment course and longer follow-up are needed to assess late toxicity.

3. Limitations

There are some key Phase II outcome limitations. Single-center studies with only 66 patients do not provide good sensitivity. The follow-up time of this trial does not allow the assessment of durable therapeutic responses or delayed complications. More importantly, there was no significant difference found in quality-of-life measurements with the EORTC QLQ-C30 [1]. This could indicate that the global measure was not sensitive enough to capture localized skin benefits, or that the six-day follow-up period was inadequate. Phase III studies can use validated RID-specific PRO measures (e.g., Skindex-16 or RISRAS), combined with current physician grading using CTCAE or RTOG.

Additionally, the trial did not report cancer types, radiation doses, or fractionation schemes, all of which significantly impact RSI severity and may influence treatment response. Radiation dermatitis varies dramatically by anatomical site (breast versus head/neck) and radiation technique, potentially affecting the generalizability of these findings.

The result of the mechanistic interpretation must also be approached with caution. Although the findings can be attributed to the PMSCs' anti-inflammatory properties and paracrine functions [4], it still has to be validated if the short-term benefits of the procedures relate to cell engraftment or merely correspond to paracrine responses. The time frame of TGF-β1 expression assessment was not provided in relation to the outcome in the clinical trial.

4. Implications and next steps

Unlike passive barrier interventions such as keratin-based formulations (which showed variable results in small randomized pilots with a feasibility focus and limited sample size) [5], PMSC hydrogels offer active cellular mechanisms, including cytokine secretion, angiogenesis promotion, and immunomodulation [4, 6]. However, comparative effectiveness cannot be established from single-arm or different-population studies. Standardized outcome frameworks and potentially head-to-head comparisons would strengthen the evidence base.

Based on this encouraging data, there is rationale for a well-powered Phase III trial with extended follow-up (minimum of 3-6 months post-intervention), inclusion of anatomically varied patients, and rigorous safety reporting. It is essential that Phase III studies include cost-effectiveness analyses, as a successful translation would not only address manufacturing scale, regulatory issues for allogenic cellular therapeutics, and cold-chain distribution issues, but also concerns about cost-effectiveness within the healthcare delivery system. If validated with significant clinical outcomes and safety, then PMSC hydrogel could potentially be evaluated in guidelines for the treatment of moderate-to-severe radiation-induced skin injuries.

The broad field of regenerative medicine encompasses research involving adipose tissue-derived or bone marrow-derived mesenchymal stem cells for various applications of wound healing. Theoretical benefits of PMSCs stem from the availability of tissue, prolific growth, and high immunomodulatory efficiency. However, comparative studies involving various sources of MSCs in patients with RSI do not exist.

5. Conclusion

The Phase II trial by Tian et al. presents an encouraging preliminary evidence that PMSC hydrogel may accelerate radiation-induced skin injuries by limiting recovery from associated pain. The finding of decreased wound progression (relative risk reduction 64%) and dermatitis severity scores, along with favorable short-term safety, supports continued clinical development. However, the single-center design, small sample size, short follow-up, and absence of cancer type/radiation details limit generalizability. Claims of practice- changing efficacy await confirmation in larger, longer-duration, multicenter trials with comprehensive patient-centered outcome measurement and thorough safety evaluation, including assessment of late fibrotic effects.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Large Language Model

None

Authors Contribution

FAR contributed to the conceptualization of the study and prepared the original draft of the manuscript. AG was involved in the conceptualization and also drafted the original manuscript. AHM

contributed to the conceptualization, prepared the original draft, and critically reviewed and edited the manuscript. SF participated in drafting, reviewing, and editing the manuscript.

Data Availability

No new data were created or analyzed in this commentary, so data sharing is not applicable. All information discussed is derived from previously published studies, which are cited in the References, and any underlying data can be accessed in those original publications.

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