



Topical Natural-Origin Polynucleotides in Radiation-Induced Skin and Mucosal Toxicity

Stefania Giudici¹, Francesca Maggio¹, Marco Bertocchi¹, Maria Rosaria Lucido¹, [Renzo Corvò](#)^{2,3}, Marco Orsatti¹

¹ *Struttura Complessa Radioterapia, Ospedale Sanremo, Asl 1 Imperiese, Sanremo, Italy*

² *IRCCS Ospedale Policlinico San Martino, Genova, Italy*

³ *DISSAL, Dipartimento delle Scienze della Salute (Health Sciences Department), Università di Genova, Genova, Italy*

This study is dedicated to the memory of Professor Renzo Corvò.

Corresponding author: Stefania Giudici, Struttura Complessa Radioterapia, Ospedale Sanremo, Asl 1 Imperiese, Via Giovanni Borea 56, 18038 Sanremo, Italy; Email: s.giudici@asl1.liguria.it

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Abstract

Seventy to 90 percent of patients who have received radiation treatment struggle with radiation skin and mucosal toxicity. The inflicted damage to progenitor cells and local microcirculation makes it more likely that wounds, infections, and fibrosis may occur; lesions of variable severity often co-exist. Acute erythema, hyperpigmentation, and mild desquamation usually wane in weeks and require only minor treatment. Conversely, the management of persistent radiation dermatitis and telangiectasia remains unsatisfactory; chronic lesions may progress to tissue atrophy and disfiguring fibrosis.

Trotophic, natural-origin polynucleotides, formulated as Class III medical devices, have long shown to be a reliable topical option to stop the progression of radiation-related lesions. The present review illustrates the rationale of polynucleotides in skin and mucosal radiodermatitis management. It also illustrates the clinical results in a series of exploratory clinical studies carried out with polynucleotide devices over the last decade. The examined studies open the way to the high-level clinical research program, which will develop over the next years.

Keywords

cancer radiotherapy, polynucleotides, radiation-induced skin reactions, radiodermatitis

Abbreviations

3D CRT: three-dimensional conformal radiation therapy;
ATM: ataxia telangiectasia mutated;
BAX: BCL2-associated X protein;
BBC3: BCL2-binding component 3;
BCL2: B-cell CLL/lymphoma 2;
BRAF: v-RAF murine sarcoma viral oncogene homolog B1;
CDKN1A: cyclin-dependent kinase inhibitor 1A;
CTCAE: common terminology criteria for adverse events;
EGFR: epidermal growth factor inhibitor;

FDXR: ferredoxin reductase;
GADD45A: growth arrest and DNA-damage-inducible, alpha;
RTOG: radiation therapy oncology group;
SESNI: sestrin 1;
TGF-β1: transforming growth factor-beta 1;
UVB: ultraviolet B radiation;
XPC: xeroderma pigmentosum, complementation group C;
ZMAT3: zinc finger, Matrin-type 3

INTRODUCTION

Radiation therapy-related toxicity, an interplay of genetics and other determinants

More than 50% of cancer patients receive radiation therapy (RT) at some stage during their illness, with almost 70-95% of the RT-treated patients developing acute or chronic, or mild to moderate to severe skin reactions. These patients are especially at high risk of developing soft tissue sarcomas and cancers of the skin, breast, head and neck, vulva, and anus: due to proximity to the target area of ionizing radiation, sparing the epidermis and subcutaneous tissues may not be straightforward.^[1,2] Irradiation of pelvic tumors like prostate or uterine cancers may also induce rectal mucosal toxicity and low life quality.^[1,2]

Genetics seems to have a role in the individual radiosensitivity and the development of adverse skin reactions. A recent paper described the association between radiation toxicity, ATM, CDKN1A, FDXR, SESN1, XPC, ZMAT3 genes expression, and the BCL2/BAX ratio.^[3] The paper also discussed how individual radiosensitivity (highly radiosensitive, radiosensitive, normal, and radioresistant) could be related to the BBC3, FDXR, GADD45A genes expression, and the BCL2/BAX ratio. These markers are variably associated with the disorders of signal transduction and DNA repair, cell cycle arrest, and apoptosis.^[3] The extension of the skin surface area exposed to radiation and concurrent radiosensitizing chemotherapy, including targeted therapy with BRAF and EGFR inhibitors, also affect the likelihood of developing dermatitis.^[1,2,4]

Administration of high-energy ionizing radiation is usually in small daily doses, delivered with 3D conformal radiotherapy or new techniques such as volumetric modulated arc therapy (VMAT) to minimize harm to healthy skin tissues and organs close to the target tumor. Nevertheless, at least some damage to the rapidly proliferating basal epidermis is almost inevitable, with skin dryness and itching as first symptoms, and desquamation and loss of the skin barrier function as an end outcome. Breakdown of skin integrity with moist weeping lesions is most likely in the inframammary fold and toward the axillary tail.

Dosimetry and clinical severity

The radiation dose administered is directly related to the radiodermatitis severity with a range of lesions often co-existing within the same radiation field.^[5] Damage to local microcirculation, leading to tissue hypoxia and fibrosis, inflammation, compounds the risk of wounds and infections. Acute skin changes occur within 90 days following RT (**Table 1**); chronic lesions usually happen only after 90 days.^[5]

Sustained hyperpigmentation does not occur until 2-4 weeks after RT, often together with a sunburn-like reaction with erythema, oedema, itching, burning sensations, and tenderness; damage to hair follicles and sebaceous glands translates into hair loss and dry skin. Dry desquamation, pruritus and skin flaking occur at cumulative RT doses above 20 gray (Gy).^[6]

Moist desquamation with a breakdown of the skin barrier function occurs at doses above 30 to 40 Gy. It may associate with painful red skin, serous exudation, hemorrhagic crusting, and possibly bullae, contact injury, mainly in flexural areas due to frictional stress, infection, and ulcers. Non-invasive laboratory assessment commonly shows the skin barrier dysfunction to precede clinical symptoms.^[6]

Acute erythema, oedema, and desquamation usually resolve two to four weeks after RT, although some residual post-inflammatory hyperpigmentation may wane only after months.^[5] According to investigations with a standard semi-quantitative instrument to assess clinical severity, the common terminology criteria for adverse events (CTCAE) version 4.0, the expected incidence of acute dermatitis after breast-conserving surgery with up-to-date radiation equipment is about 3% grade 0, 35% grade 1, 60% grade 2, and 2% grade 3.^[6]

Skin atrophy, stiffness and fibrosis are the markers of chronic radiodermatitis after the acute phase; the same is valid for skin hypo- or hyperpigmentation and the loss of sebaceous glands, hair follicles and nails. Dilated neo-vessels form telangiectasia, while tissue hypoxia may cause chronic wounds and ulcerations.^[4,5] Non-melanoma skin cancers and angiosarcomas are rare sequelae of chronic radiation dermatitis.^[5]

All radiation-induced chronic lesions are the outcome of aberrant regulation of pro-fibrotic cytokines leading to stromal cell dysfunction, dysregulated re-modeling of the

Table 1. Symptoms and dose-related, first time of onset of acute radiation toxicity

Symptoms and timing of acute radiation dermatitis		
Skin reaction	Time of onset after RT	Radiation dose at onset
Erythema and hyperpigmentation	1 to 2 weeks	10-40 Gy
Dry desquamation	3 to 4 weeks	20 to 30 Gy
Moist desquamation	More than four weeks	30 to 40 Gy

Gy=gray^[5]

extracellular matrix, and fibrosis (**Fig. 1**); increased transforming growth factor-beta 1 (TGF-β1) dermal levels most likely have a role.^[5,7-9] **Figs 2, 3** illustrate some examples of acute and chronic lesions.^[5,9]

Chronic RT damage, really a persisting medical need?

RT may negatively influence life quality, with the most significant impact resulting from severe radiodermatitis.^[10] Water-soluble skin moisturizers may suffice with Grade-1 and Grade-2 dermatitis; petroleum-based emollients are helpful when dryness, skin pain, and dry desquamation worsen. Weak-strength hydrocortisone 1% cream is useful to control papular eruptions and minor itching, possibly in association with anaesthetic jelly. Non-stick dressings such as aluminum acetate water solutions or silver sulfadiazine creams may help manage moist desquamation^[11,12]; photobiomodulation may also be helpful^[13].

The hard problem is chronic radiation-induced dermatitis, which can progress to extensive fibrosis.^[6] Telangiectasia may (somewhat) benefit from pulse dye laser therapy, while chronic post-irradiation wounds usually need silver-based or absorbent dressings because of compromised local microcirculation. Necrosis and severe ulceration may need debriding and surgery.^[6] Drug care, hyperbaric oxygen, laser therapy, supportive pain management, and psychological and cosmetic interventions may help with the challenge, chronic fibrosis.^[4]

Unfortunately, according to the International Society of Dermatology, as late as 2017, none of the many topical agents and specialized wound dressings showed any con-

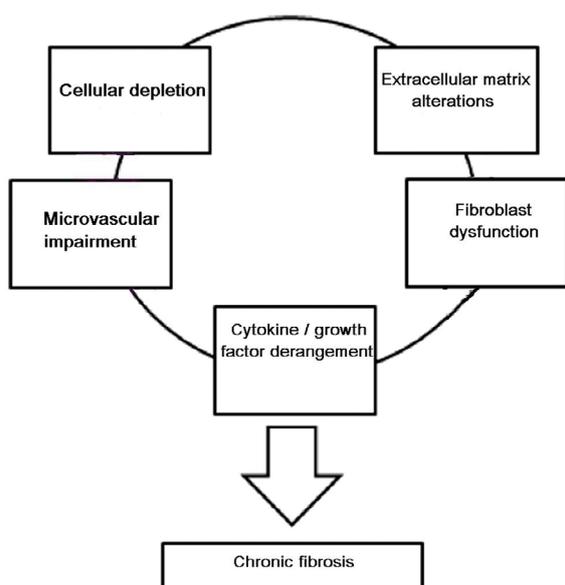


Figure 1. The events in chronic radiation-induced skin and mucosal aberrations are similar to what happens in fibrotic diseases affecting the heart, skin, lungs, kidneys, and other organs. TGF-β1 increased levels in irradiated tissues is likely to act as the main pro-fibrotic cytokine growth factor.^[5]



Figure 2. (Up) Grade-1 faint, diffuse chest wall erythema with Grade-4 axillary focus of necrosis following RT after mastectomy surgery. (Down) Acute forearm ulcer with severe diffuse erythema, patchy moist desquamation and prominent telangiectasia following RT for osteosarcoma. Source: DermNet NZ dermatology images database, dues paid.



Figure 3. Chronic non-healing ulcerated wound after mediastinal RT. Source: DermNet NZ dermatology images database, dues paid.

sistent efficacy to help prevent and manage RT-associated toxicity, especially chronic sequelae.^[1]

Local application of natural-origin polynucleotides has emerged as a promising strategy for treating acute radio-dermatitis and preventing chronic sequelae.

The rationale for polynucleotides in the prevention and treatment of RT-induced skin and mucosal disorders

Polynucleotides are physiological and ubiquitous molecules in all tissues, including skin and mucosae; damaged or dying cells and local hypoxia physiologically lead to polynucleotide derivatives release in tissues.^[14,15]

Polynucleotides associate marked lenitive and hydrating properties with a trophic activity on sub-epithelial fibroblasts in skin and mucosae. The highly hydrated tri-dimensional structure that polynucleotides develop in tissues enhances their moisturizing properties.^[16] Studies with other polynucleotide-based formulations support the polynucleotide trophic activity in anal fissures, the vulvo-vaginal skin and mucosa and pelvic tissues.^[17] The same is true for investigations in other disorders with massive tissue loss like the venous ulcers of lower limbs, diabetic feet, and the general healing of torpid wounds.^[18,19] In all these conditions with tissue loss, the intralesional treatment with polynucleotides re-ignites the wound healing process and accelerates it.^[18,19]

The key of the polynucleotides value is replenishing the tissue reservoirs of metabolic precursors, leading to fibroblast activation after polynucleotides release in the wound bed. Fibroblast activation accelerates skin and mucosal healing, ignited by local hypoxia and damaged or dying cells, by priming fibroblasts to produce new collagen and elastin fibers and new matrix glycosaminoglycans.^[20-22] The increase in elastin fibers is distinctive, e.g., +21.8% of skin elasticity under stress in one study.^[21] Polynucleotides also mitigate radiation-related erythema by acting as free radical scavengers and antioxidants, as shown in subjects exposed to ultraviolet A and B radiation (290–400 nm).^[23] These properties associate with high safety and compliance of treated subjects, without significant side effects other than occasional transient erythema.^[24]

Clinical experience with polynucleotides in the prevention of RT-induced acute and chronic skin and mucosal disorders

The earliest exploratory studies about the protective potential by polynucleotides against the skin and mucosal RT toxicity originated from early in vivo and in vitro evidence about these agents and ultraviolet radiation toxicity such as lack of severe acute UVB lesions in individuals with low Fitzpatrick skin phototype and low cell toxicity in cultured UV-exposed fibroblasts.^[25,26]

Ten female patients with breast cancers undergoing adjuvant radiotherapy and 14 male patients undergoing radi-

cal radiotherapy for prostate cancer participated in the earliest pilot investigation in human subjects.^[27] Breast cancer women received a total of 50 Gy X-rays in 25 RT sessions over five weeks; male patients with prostate cancer received 78 Gy in 38 RT sessions over 7.5 weeks. The twice-daily polynucleotide topical treatment aimed to prevent or reduce, respectively, acute skin radiodermatitis (Leni-Radio[®] cream) and 2+ rectal toxicity (Leni-Radio[®] Rectal Gel, 5 mL/die). Applications in the two pilot cohorts began the same day of the first RT session and went on until two weeks after the last RT session. Six out of 10 breast cancer patients experienced RTOG Grade-2 skin toxicity with no episode of Grade-3 lesions. Conversely, no prostate cancer patient experienced Grade-2+ acute rectal mucositis, and there were just two cases of Grade-1 proctitis.^[27]

There were more experiences after these very first ones over the next few years. Sixty pT1/T2, N0/N+, M0 breast cancer women patients received 46 Gy in four weekly sessions for five weeks with an additional weekly 1.2 Gy-photon boost. They also received the polynucleotide-based cream twice daily until complete disappearance of all skin lesions.^[28,29] As regards the polynucleotide gel formulation, 50 prostate cancer patients (58-78 years old) received it together with 75 Gy RT fractioned in 30-38 five-weekly sessions (radical RT in 43, adjuvant RT in 7; no chemotherapy).^[30]

At the end of the RT cycle, 54% of women showed NCIC Grade 0-1 RT skin toxicity; 33.5% showed Grade-2 toxicity and 12.5% Grade-3 acute skin lesions without differences between women who had undergone chemotherapy or hormonal therapy. After one month, 52% of women showed no toxicity (Grade 0), 41% showed Grade-1 skin lesions, and only 7% still showed Grade-2 toxicity.^[29]

As regards the prostate cancer patients, only one out of 50 gel-treated subjects showed some modest proctitis (scores: 0.43 out of a maximum of 2 at the end of the RT treatment cycle and 0.29 after 1 month of follow-up) with very mild and transient perianal skin toxicity (score at early evaluation: 0.17 out of a maximum of 3).^[30]

In conclusion, those very early exploratory experiences demonstrated a very low incidence of RT-induced lesions of the skin and rectal mucosa together with lack of high-grade toxicity. Polynucleotides appeared to be a viable and sound option to prevent RT skin and mucosal toxicity and control and keep at low grade those lesions that could arise, in agreement with the rationale of associating their moisturizing efficacy with their reactivation of dermal and mucosal fibroblasts. The following years saw an extended program of exploratory studies in hundreds of patients.

The extensive RT experience with topical polynucleotides over the more recent years

The results of a first extensive study in 497 pT1/T2, N0/N+, M0 breast cancer patients appeared in 2010. All participating women received twice-daily treatment (morning

and evening) with topical polynucleotides (Leni-Radio® Cream) since the day of the first adjuvant RT session until four weeks after the end of the RT cycle.^[31,32] All women completed the polynucleotide preventive program, with 54% of women showing NCIC Grade 0-1 skin toxicity at the end of RT, i.e., 46 Gy in 4 weekly sessions over five weeks to the whole breast through two tangential fields with an additional weekly 1.2 Gy-photon boost. The lack of toxicity increased to 86% after one month of further follow-up (Fig. 4). Forty-six percent of women had received chemotherapy (anthracyclines or taxanes); 74% hormone therapy (tamoxifen or aromatase inhibitors). All women showed negative surgical margins and had chest X-ray, abdominal ultrasound and bone scan performed before treatment. A group of independent radiotherapists evaluated skin toxicity according to NCIC criteria.^[32]

No Grade-4 toxicity appeared during and after treatment. Leni-Radio® cream was highly successful in the long-term prevention of skin toxicity, with 92% of women showing NCIC Grade 0-1 skin toxicity after six months, 6% showing G2 skin lesions and 2% of women still showing severe G3 skin toxicity. After one year of follow-up, 7% and 3% of women showed chronic G2 and G3 skin toxicity, once again with no difference in incidence or severity in women who had undergone chemotherapy or hormonal therapy.^[32]

The next year, an open study in 36 elderly breast cancer patients (more than 65 years old; mean 74, range 65-87) confirmed the satisfactory cosmetic outcomes and the high safety of Leni-Radio® cream as a preventive treatment of skin radiation toxicity.^[33] Those older women underwent hypo-fractionated adjuvant RT (39 Gy over four weeks in 13 fractions plus a weekly 1.0-Gy boost) after conservative

surgery (67% quadrantectomy plus sentinel node procedure, 22% quadrantectomy plus axillary nodal dissection, 8% lumpectomy plus sentinel node procedure, 3% lumpectomy alone). Six women (17%) had received adjuvant chemotherapy (anthracyclines or taxanes) with a mean overall 6-month RT delay (the median RT delay was 69 days in women who had not received chemotherapy).^[33]

No elderly patient of the polynucleotide-treated cohort showed more than Grade-1 or Grade-2 skin toxicity after one month (Fig. 5), with no differences in women who had previously received chemotherapy, and no long-term fibrosis. Most older women appreciated the short RT period (3 weeks) and the lack of significant skin toxicity after one month.^[33]

In 2013, the results appeared of a study performed in 300 breast cancer patients randomized to post-RT twice-daily local application of Leni-Radio®, a commercial cream (β-glucan, alginates, and hyaluronic acid) and a lenitive and protective galenic formulation (calendula, A and E vitamins, and linoleic and linolenic acid essential fatty acids; 100 women per group).^[34] The polynucleotide application began with the first RT session and ended with the last session. All women received a total radiation dose of 50 Gy (2 Gy per 3D-CRT fraction) and an electron boost (10-16 Gy) with a 4 and 6 MEV linear accelerator. A fraction variable from 26 to 30 per cent of women in each treatment group had received post-surgical chemotherapy. More than Grade-2 toxicity allowed polynucleotide withdrawal or supplementation with topical triamcinolone. No woman developed skin toxicity more severe than Grade 2 or dropped out because of side effects. In contrast, one-third of treated women showed no skin toxicity at the end of the RT cycle, a

Short-term skin toxicity

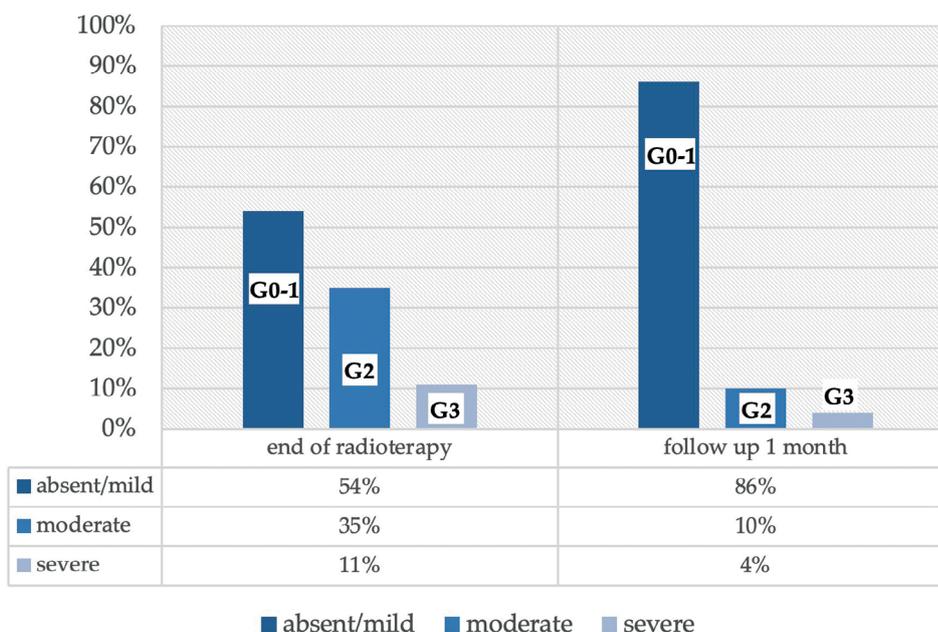


Figure 4. Incidence and severity of RT-induced skin lesions at the end of the RT sessions and after one further month of follow-up (TURNOVER® is another brand in some countries).^[32]

more favorable outcome than comparators (Fig. 6).^[34]

Table 2 shows the Grade-0, Grade-1 and Grade-2 toxicity profiles at the end of RT sessions. Grade-1 and Grade-2 toxicity in 81% of the 300 breast cancer patients who had

previously received chemotherapy compared with 73% of women who had not).^[34]

Polynucleotide-based Leni-Radio® favorably compared with other agents in women formerly treated with che-

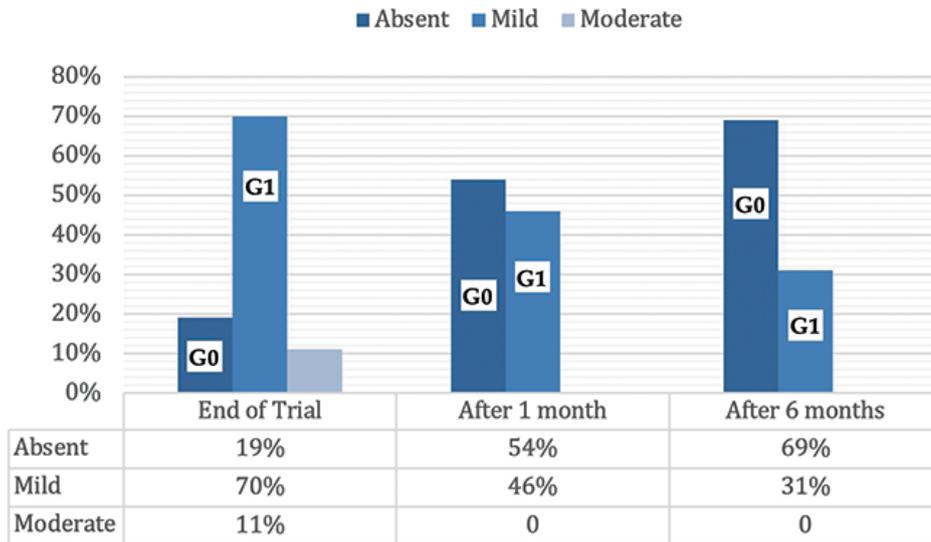


Figure 5. Incidence and severity of RT-induced skin lesions at the end of the RT sessions and after one further month of follow-up (TURNOVER® is another brand in some countries).^[33]

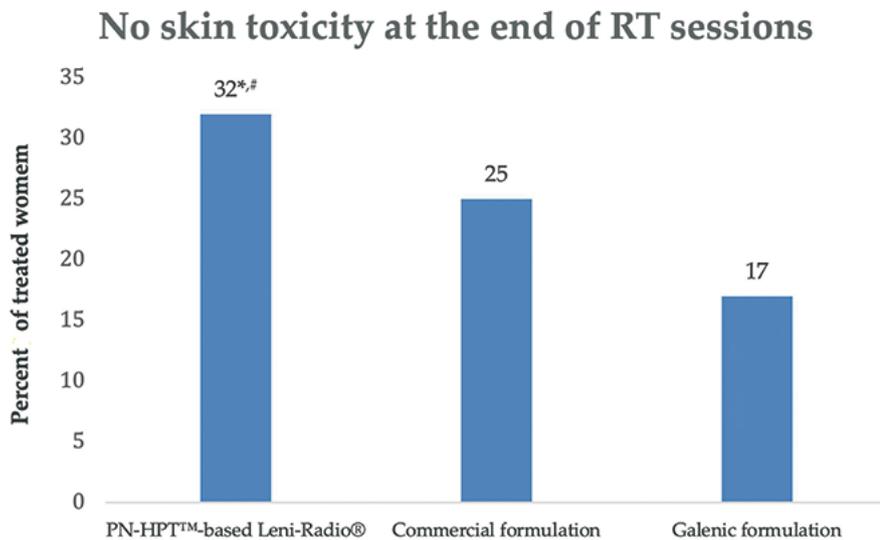


Figure 6. Percentage of 300 polynucleotide-treated women with evidence of no skin toxicity (G0) at the end of the RT sessions. Commercial formulation: based on β-glucan, alginates and hyaluronic acid; galenic formulation based on calendula, vitamins and essential fatty acids. * $p < 0.05$ vs. commercial formulation; # $p < 0.01$ vs. galenic formulation (TURNOVER® is another brand in some countries).^[34]

Table 2. Severity of RT-related skin toxicity, if any, at the end of the RT sessions; per cent of treated women in each treatment group

Skin toxicity	Skin toxicity at the radiotherapy treatment cycle		
	None (G0)	Mild (G1)	Moderate (G2)
Polynucleotide-based Leni-Radio®	32%*,#	56%	11%
Commercial formulation	25%	60%	15%
Galenic formulation	17%	58%	25%

* $p < 0.05$ for polynucleotide-based Leni-Radio® vs. commercial formulation; # $p < 0.01$ vs. galenic formulation.^[34]

motherapy. Grade-1 and Grade-2 toxicity developed in 61% and 3.8% of treated with Leni-Radio[®], 73% and 23% of women treated with the β -glucan, alginates, hyaluronic acid formulation, and in 63% and 17% of women treated with the lenitive and protective galenic formulation. Fourteen per cent of the polynucleotide-treated women had to resort to the triamcinolone cream vs. 15% of the women treated with the commercial formulation and 39% treated with the galenic formulation.^[34]

CONCLUSIONS

The optimal care of RT-induced toxicity is still a partially unmet medical need. Acute reactions are often troublesome and may evolve into chronic lesions which, when severe, are disfiguring and aesthetically and psychologically devastating.^[35-37]

The rationale to leverage the well-known trophic properties exerted by polynucleotides on dermal and mucosal fibroblasts is solid and substantiated by a wealth of preclinical studies. The same is true for the hydrating, moisturizing, and elasticizing properties enjoyed by polynucleotides. The extended program of exploratory and extensive studies herein illustrated supports the rationale; it is also the basis for the vast comparative clinical research program beginning in Europe. Preventing RT-induced lesions is especially important for radiotherapists aiming to complete their RT programs without excluding patients with increased RT toxicity risks because of previous adjuvant chemotherapy.

Summarizing the pieces of evidence accumulated so far, prevention of severe Grade-4 acute toxicity was complete in hundreds of patients treated with topical polynucleotides since the first RT session until either the last RT session or for one more month of follow-up. Episodes of long-term persistence after 6 and 12 months were only occasional.^[32] Even when persistent, chronic toxicity was almost always mild: 6-7% of Grade 2 and only 2-3% of Grade-3 toxicity 6 and 12 months after starting RT.^[32] Short-term aesthetic outcomes also appear to be favorable for Leni-Radio[®] compared with current options. TURNOVER[®] in some countries is a second proprietary brand for the same polynucleotide formulation in some countries.

Unsurprisingly, Leni-Radio[®] (TURNOVER[®]) and topical polynucleotides are useful when the loss of epithelia or stretch marks are the problem or, in specific gel formulations, to treat anal rhagades and, in general, anal and perianal inflammations and proctitis. Of course, the polynucleotide-based cream or gel application should be correct: no more than the needed quantity of gel or abundant amount of cream at least twice daily on RT-related lesions, even with damaged or lost epithelium and ulcers. Treatment should go on until complete reversal of all skin or mucosal lesions.

As protection and prevention, once-daily application of Leni-Radio[®] or TURNOVER[®] (twice daily with the cream formulation) should begin one or two days before the first RT session. However, only the adequately designed stud-

ies now beginning will conclusively define the promising role of topical polynucleotides in preventing RT-associated acute and chronic lesions and the treatment of already established skin and mucosal RT toxicity.

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Competing interests

The authors have no support to report.

Data resources

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Author contributions

Under the general supervision of Prof. Renzo Corvò, Full Professor of Radiotherapy at the University of Genoa Medical School (Corresponding Author), all other authors collaborated to the submitted manuscript by writing the sections that discuss their previous exploratory studies and clinical contributions.

Prof. Renzo Corvò wrote the general introductory chapters, including the rationale for using polynucleotides in preventing and treating radiation-induced skin and mucosal toxicity. Prof. Renzo Corvò is also personally accountable for the accuracy and integrity of the clinical and editorial work leading to the manuscript's submission to Folia Medica. All authors reviewed the content of the manuscript and consent to publication. The document does not contain data from any person, and specific permissions are "Not applicable".

Author Information Note

Sadly, the author Professor Renzo Corvò, one of the most distinguished academic radiotherapists in Italy and Europe

and President of the Italian Society of Radiotherapy, died suddenly on October 3, 2021. This article is dedicated to his cherished memory.

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Полинуклеотиды природного происхождения для местного применения при радиационно-индуцированной токсичности кожи и слизистых оболочек

Стефания Джудичи¹, Франческа Маджио¹, Марко Берточи¹, Мария Росария Лучидо¹, Ренцо Корво^{2,3}, Марко Орсати¹

¹ Кафедра лучевой диагностики и лучевой терапии, Больница Сан Ремо, Сан Ремо, Италия

² Многопрофильная больница „Сан Мартин“, Генуя, Италия

³ Кафедра медицинских наук, Университет Генуи, Генуя, Италия

Это исследование посвящено памяти профессора Ренцо Корво.

Адрес для корреспонденции: Стефания Джудичи, Кафедра лучевой диагностики и лучевой терапии, Больница Сан Ремо, ул. „Джовани Боре“ № 56, 18038 Сан Ремо, Италия; Email: s.giudici@asl1.liguria.it

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Резюме

От семидесяти до 90 процентов пациентов, прошедших лучевую терапию, борются с лучевой токсичностью кожи и слизистых оболочек. Нанесённое повреждение клеток-предшественников и местной микроциркуляции повышает вероятность возникновения ран, инфекций и фиброза; поражения различной степени тяжести часто сосуществуют. Острая эритема, гиперпигментация и лёгкое шелушение обычно исчезают в течение нескольких недель и требуют лишь незначительного лечения. И наоборот, лечение стойкого лучевого дерматита и телеангиэктазий остаётся неудовлетворительным; хронические поражения могут прогрессировать до атрофии тканей и обезображивающего фиброза.

Протрофические полинуклеотиды природного происхождения, разработанные в качестве медицинских препаратов класса III, уже давно показали себя как надёжный местный вариант для остановки прогрессирования поражений, связанных с облучением. Настоящий обзор иллюстрирует целесообразность применения полинуклеотидов при лечении радиодерматита кожи и слизистых оболочек. Он также иллюстрирует клинические результаты серии поисковых клинических исследований, проведённых с полинуклеотидными препаратами за последнее десятилетие. Рассмотренные исследования открывают путь к программе клинических исследований высокого уровня, которая будет развиваться в течение следующих лет.

Ключевые слова

лучевая терапия рака, полинуклеотиды, лучевые кожные реакции, радиодерматит
