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REVIEW ARTICLE

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A Parallel, Observer Blind Study of the Skin Protection Properties of Silicone-Based Gels after Radiotherapy Exposure

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ABSTRACT

Objective: Radiotherapy of cancers are usually accompanied by some form of radiation induced skin toxicity (radiation dermatitis) in most patients receiving this type of treatment. It can vary from very mild disease to extensive and severe dermatitis limiting further treatment. It is therefore obvious that preventative care will optimise the outcome of radiation of the tumour while the skin's integrity is preserved leading to a better clinical outcome overall.

Methods: In Vitro: In the study a newly developed silicone topical device (RT-Gel Sun Pharma South Africa), is compared to a similar product StrataXRT as well as to a negative control group of no gel. Gels were tested to observe the effect on the radiation dose provided. All gels were applied as a thin layer to the surface of the bolus within the Farmer Chamber.

In Vivo: In this multicentre study a newly developed silicone topical device (RT-Gel® Sun Pharma South Africa), applied as a thin layer gel, is compared to a similar product StrataXRT as well as to standard of care in practice. The aim was to compare patients' preferences of treatment modalities as well as establishing differences in clinical outcomes focussing on grades of skin toxicity after radiation therapy. Patients were recruited at radiation oncology sites after being prescribed radiation dosages with curative intent for mostly breast and head and neck cancers.

Results: In Vitro: The uncertainties pertaining to the theoretical dose changes and radiation measurements indicates clearly the differences caused by the application of a silicone-based gel during radiotherapy is small enough to be regarded as negligible.

In Vivo: The primary outcomes demonstrate the patient's satisfaction with RT-Gel® i.e. a significant preference for RT-Gel compared to both StrataXRT® ($p < 0.02$) and standard of care ($p < 0.001$). The clinicians' toxicity scores also favoured RT-Gel® over StrataXRT ($p < 0.04$ ANOVA).

Conclusion: It can thus be concluded that preventative treatment with RT-Gel® is at least as effective if not better than competitors, well tolerated and preferred by patients. . It furthermore indicates that dose is not affected by gel and that washing of treated area before next treatment is not required to "prevent build-up of gel".

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RT-Gel, StrataXRT, Radiation Dermatitis, Skin Toxicity

Introduction

Radiation therapy is a widely used and accepted form of treatment for various different types of cancer, unfortunately with the use of radiation comes the adverse effect of radiation induced skin toxicity (radiation dermatitis) which occurs in most patients receiving this type of treatment [1-4]. Salvo et al reported that around 90% of patients treated with a localised external radiation beam are most likely to develop skin reactions at the locally treated area. Radiation dermatitis involves a complex pattern of direct tissue injury such as intense damage to cells of the epidermis as well as the endothelial cells within the walls of blood vessels, with resultant inflammatory cell recruitment [1].

Radiation dermatitis (RD) is known to generally manifest as quickly as within a few days and weeks post the start of radiotherapy treatment. RD is most typically confined to the irradiated areas of skin. Acute radiation dermatitis occurs within 90 days of exposure to radiation, whereas late injury presents months to years after radiation exposure [1]. The effects of RD ranges from mild to moderate (grades 1 and 2), however, some patients may have a more pronounced reaction (Grades 2-4), Table 1 [2, 3]. The incidence of severe reactions is not only dependent on treatment related factors such as the total radiation dose, the dose per

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fraction, the overall treatment time, beam type and energy and the surface area of the skin that is exposed to radiation, but is also influenced by the patient's general skin condition, nutritional status, chrono-aging, photo-aging and co-morbidities [2-4]. Adding chemotherapy or immunomodulatory agents to the radiotherapy regime increases the acute side-effect profile of treatment [2, 4, 5].

Table 1: Toxicity grading of radiation dermatitis based on the National Institutes of Health Common Toxicity Criteria-Adverse Event (CTCAE) outlined by Bernier et al. and Ryan

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
None	Faint erythema or dry desquamation.	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema.	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion.	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site.	Death

Pain and other adverse effects associated with RD has a negative effect on the quality of a patient's life, which often leads to interruption of radiotherapy, which in turn may impair control of disease [1, 5].

A range of products as well as specialised practices are utilised to manage patients with acute RD, with limited success. The best management of acute RD is to induce prophylactic measures as far as possible, this may include gentle washing and drying of the skin with mild soap or detergents, the application of a variety of topical creams to potentially reduce skin inflammation and wound dressings or barrier films to keep the skin intact [2, 3, 6].

Management of an acute skin reaction may be based on the severity of the reaction and includes the use of aqueous creams, calendula ointment, corticosteroid creams, antibacterial moisturisers or topical antibiotics, chlorhexidine-based creams, drying gels, anti-inflammatory emulsions, sucralfate and the application of dressings to the irradiated areas [2, 3, 6]. The number of effective treatments for the prophylaxis and management of acute RD are extremely limited. Most studies found that topical treatment only provides some degree of relief in acute RD, with little to no evidence to support the use of one topical approach over another [3, 4, 6, 7]. Kumar et al, reported that products which maintain the skin's moisture level and integrity is most helpful in reducing the severity of skin related Adverse Events (AEs). Furthermore, the use of mild soap and gentle washing during radiotherapy is routinely employed, while several studies disagree on its effectiveness as a prophylactic measure in the prevention of acute RD [2, 3, 6]. The study by Ryan (2012) suggested that "control of inflammatory waves, improved wound healing, and stabilisation of skin barrier is imperative to minimising radiation-induced skin injury from localised radiation exposure".

Pathophysiology of Radiation Dermatitis

After initiation of radiation treatment, damage occurs immediately to the basal keratinocytes as well as the hair follicle stem cells while reactive oxygen species (ROS) are generated [1, 6]. The subsequent fraction of radiation generates inflammatory cell recruitment and thus hampers the epidermal cells' ability to recover and repair tissue or DNA damage.

Keratinocytes, fibroblasts, and endothelial cells in the skin stimulate resident Langerhans cells, mast cells, T cells and the trans-endothelial migration of circulating immune cells [1]. The immune competent cells present in the, release inflammatory mediators such as histamine, cytokines and lipid mediators which give rise to the symptoms associated with inflammation [8]. With the increase in vascular permeability that follows, and the chemo-attractants released by the resident cells, leukocyte infiltration is triggered.

At this stage neutrophils continue to release ROS and several lysosomal enzymes in the attempt to clear the damaged tissue and inflammatory debris [1, 9-11]. Monocytes, attracted to the inflammatory lesion by a variety of chemo-attractants, undergo a phenotypic change into macrophages and release additional pro-inflammatory cytokines and growth factors to continue the cascade of events involved in the healing process, recruiting fibroblasts and endothelial cells to the inflammatory lesion [12-14].

Lymphocytes modulate later lymphocyte traffic by the release of chemokines and inflammatory cytokines, especially interferon-gamma (IFN-ɣ) [15]. Fibroblasts, stimulated by various growth factors and cytokines produce fibrotic tissue which is characteristically seen in late injury [1].

It is thus obvious that a treatment is needed that can reduce the likely hood of skin induced damage and which can also treat established RD. This will only be achievable if the treatment can address a myriad of pro-inflammatory processes by reducing the initial impact of the radiation insult and the subsequent cellular response.

Silicone-Based Gels

Silicone-based adhesives in the form of a topical gel or gel sheeting is commonly used during cutaneous wound healing to prevent the formation of a scar [16-18]. It is believed that silicone-based adhesives improve the occlusion and hydration to the wound bed, increase the hydration of the stratum corneum and also increase the skin's surface temperature, which in turn improves wound healing and prevents the formation of a scar [19].

StrataXRT is an innovative, flexible silicone gel wound dressing, marketed for the prevention and treatment of RD [20]. Developed with the aim of creating a self-drying, non-stick, transparent gel which has the ability to lightly bond to the most superficial layers of the skin, protecting the fragile acid mantle, while allowing for optimal hydration and reducing the skin's acute inflammatory response. The sterile semi-occlusive dressing is permeable to gas but not fluids, promoting a moist wound healing environment.

RT-Gel® (Sun Pharma, South Africa) is specifically developed to prevent and or treat RD, and medical-therapeutic burns (e.g. laser, or chemically induced). It is a sterile medical silicone device which

does not alter radiation treatment or change dose even when applied to the skin during treatment (applied as a single agent). RT-Gel® is a semi-occlusive (breathable) layer which can increase and maintain skin integrity while enhancing the healing process (re-epithelialisation).

The aim of the present study was to compare RT-Gel® with StrataXRT® and the best standard of care in practice. The primary outcomes being the patients' preferences of treatment modalities as well as in clinicians scoring of the grade of radiation induced skin toxicity during radiation therapy.

Methods

In Vitro

During this experiment a Siemens Primus linear accelerator was used to produce a constant output of radiation, set at 100 monitor units (MU) calibrated to 1cGy per MU. Equipment used to measure the radiation output was a 0.6cc Farmer Chamber with a Unidos® Electrometer placed in/under various depths of Perspex's sheets (density of 1.15g/cm^3). The linear accelerator used in the experiment to provided photon energies (6MV & 15MV) as well as electron energies (6MeV, 9MeV, 12MeV & 15MeV).To ensure sufficient build-up of radiation at the level of the ionization chamber when using photon energies, a setup of 99.5cm source to surface distance (SSD) with 3.7cm Perspex + 6mm of bolus was chosen. The electron energies used in this study were performed according to two different setups. This is due to the differences in depth of maximum dose (dmax) as well as the dose fall-off differing substantially between the energies. The setup for the 6MeV was 100cm SSD with 0.7cm Perspex + 0.6cm bolus. For the remaining energies 9MeV, 12MeV and 15MeV a setup of 100cm SSD with 1.7cm Perspex and 0.6cm bolus was used. During all radiation exposures a standard of 10cm x 10cm field size was accepted. To analyze the effects of the different gels on the radiation dose given, different gels were tested namely: StrataXRT and RT-Gel®. The silicone-based gels were applied to the surface of the bolus chamber during the experiment.

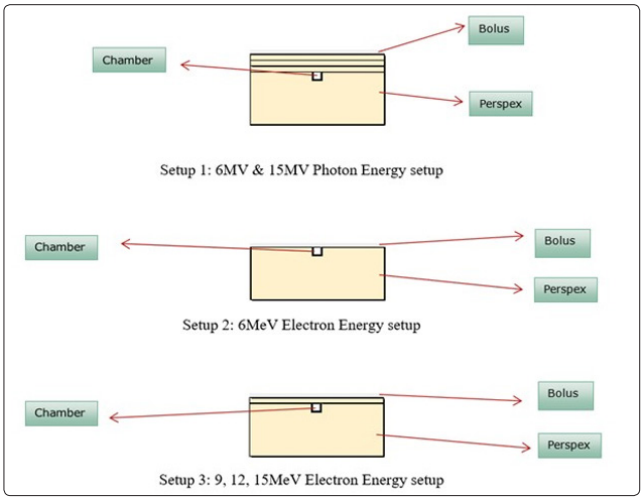

Figure 1: Diagram of Photon energy setup according to Electron energies

In Vivo

After Ethics Committee Approval (SAMA Research Ethics Committee) potential patients were identified by the study site personnel and recruited into the study once informed consent was obtained. Patients were pre-screened for specific criteria required for eligible participation in the study. Patients, who were allocated to receive radiotherapy (especially to head and neck and breast) were recruited for the study and randomly assigned to one of the 3 treatment arms (RT-Gel®, StrataXRT® or standard of care; (n=45)). Randomisation was done centrally, and trial product dispensed on pre-identified numbers to ensure block balancing within a multisite study in South Africa. This was an open label, parallel study wherein the doctors scoring the patients were blinded to the therapeutic regimen.

Application of study products

Recruited patients were thoroughly educated about the specific treatment regime prior to the commencement of the study. Patients allocated to treatment arms containing research silicones were initiated into the treatment period by applying one of the study products on the first day of an allocated radiotherapy session, this was done before the start of the session. Participants were encouraged to maintain the silicones in continuous contact with the skin (24hrs/day), therefore requiring an application more than once a day e.g., after washing the area. A very thin layer (almost not visible after application with no residue) of the study products were applied on clean, dry skin, and allowed to dry to form a thin, flexible wound dressing. The products were allowed to dry within 5-6 min, if an excess of product was applied to the treatment area, it was gently cleaned with a paper tissue or gauze.

Patients allocated to treatment arm "best alternative standard of care" received the best standard of care based on practice standards and as outlined by the study site.

Visit points

Participants were assessed according to a blind study arm allocation, (the researcher had no knowledge of the product applied), at the start of each visit and at an additional follow up visit after completion of radiotherapy as routinely scheduled by the practice. If the participant was unable to return for an on-site follow-up visit (i.e. after last treatment session), then the follow-up was conducted telephonically. (Day 0 = consent and before RD; Visit 2 = day 14; Visit 3 = day 28; Visit 4 = final on last day of RD; Visit 5 = day 60-90 follow-up; unscheduled visits were scheduled once dermatitis developed at any day)

Data collection and scoring of Radiation Dermatitis

Researchers blinded to the study modality of each participant scored the degree of skin deterioration (from grade 0 to 5), comparing the silicones with the best alternative standard of care and comparing on a worksheet based on the CTCAE outlined in Table 1. Scoring started on t = 0 and continued for 60-90 days or until no further improvement was seen. Scoring was performed both before the application of the study products as well as on days receiving radiotherapy marked as such.

Investigators were asked to photograph the skin section on t = 0 i.e. the skin area to be irradiated. At each visit as well as at unscheduled visits, if done, standardised photographs were

taken on the irradiated skin before radiotherapy at each visit. Participants were required to remove any silicone before the photographs were taken. The silicones were the reapplied before radiotherapy.

Investigators blinded to the study allocation were able to score the dermal integrity based on the CTCAE outlined in Table 1 before each scheduled visit or when the participant returned to the practice due to local skin problem e.g. radiation dermatitis specific for an unscheduled visit.

Patients scored the degree of skin deterioration on a visual analogue scale (VAS) based on the appearance (tender, irritated, itchy or burning), integrity (is the skin peeling, is it dry or flaky or wet) and colour (redness), with weekly reflexions. VAS is a simple 10 cm line on, anchored with score 0 (little to no) on the left and score 10 (severe) on the right. The participant's preference and tolerability of the different treatment modalities was assessed on a 5-point Likert scale. These patient specific scores were aggregated into a Total Satisfaction score for assessment and statistical analyses of data.

Compliance was assessed based on patient diary cards and noting the weight of the returned containers at the end of the study period.

No restrictions were provided to concomitant therapy during the course of the study, except application of products such as lotions, ointments, salves or wound dressings other than the study products or as described as the best practice standard of care. Requirement of any additional local therapy signalled the study endpoint for that patient.

Results

In Vitro

Due to linear accelerator and ionization chamber stability in measuring radiation there is a ≤0.25% uncertainty in all measurements. The study shows measurements taken in Fig 2 which reflect a maximum deviation of 0.23%. This is within the degree of uncertainty of the measuring equipment and linear accelerator output thus this cannot be justified as the cause of the gels being present or not.

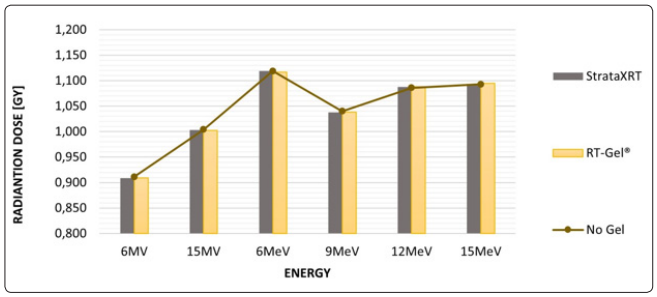

Figure 2: Dose measurements of with or without gel present

In Vivo

The silicone gels, RT-Gel® and StrataXRT®, clearly outperformed the practices' standard of care with regards to patient Total Satisfaction Score i.e. satisfaction, tolerance and preference by patients. Fifteen patients on RT-Gel®, 14 on StrataXRT®, and 10 on standard of care completed the study. RT-Gel® also significantly reduced radiation toxicity on the skin as measured by the doctor compared to StrataXRT® (p< 0,04) (ANOVA). Due to low completion rate of patients on standard of care as a result of early termination and introduction of alternative care, skin toxicity could not be reliably compared between silicones and standard of care.

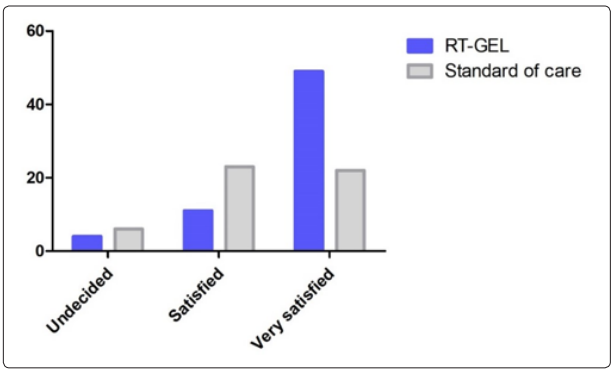

Figure 3: Patient Total Satisfaction score with prevention of skin deterioration when treating with RT-Gel® vs standard of care (p< 0.001 (Chi Square))

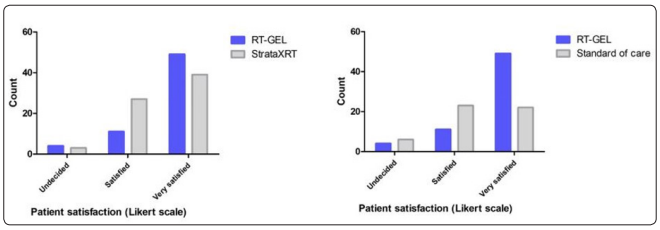

Figure 4: Patient Total Satisfaction score with prevention of skin deterioration when treating with RT-Gel® vs StrataXRT® (p < 0.02 (Chi Square))

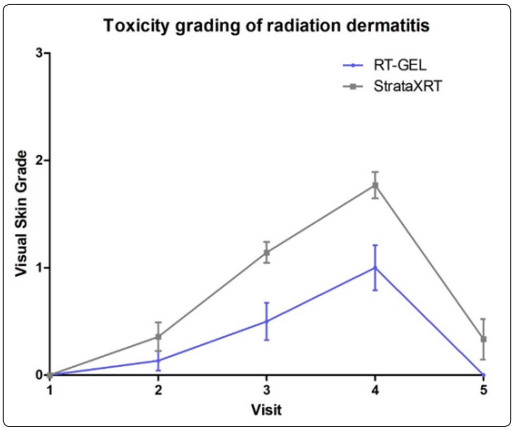

Figure 5: The effect of treatment in preventing radiation dermatitis: Skin Toxicity Grading (p< 0.04 ANOVA)

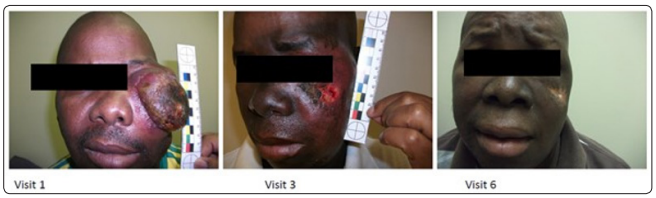

Figure 6: Results observed using silicone-based gel Patient A

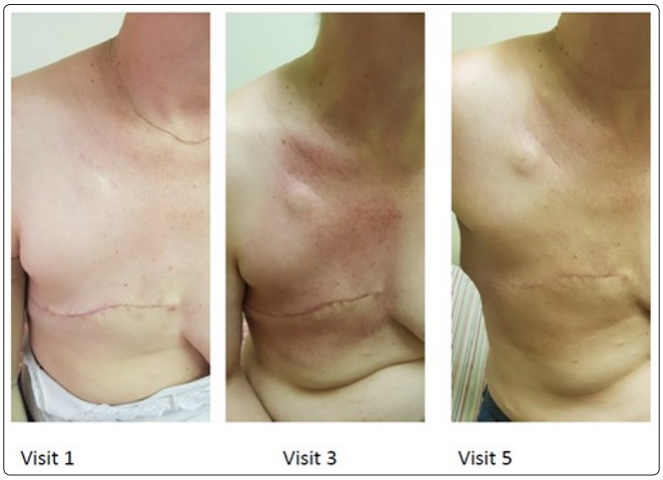

Figure 7: Results observed using silicone-based gel Patient B

Discussion

In Vitro

The uncertainties pertaining to the theorical dose changes and radiation measurements indicate that the differences caused by the gels during radiotherapy are small enough to be regarded as negligible. This is because a maximum dose attenuation of 0.09% can be expected on a 4MeV energy where patient quality assurance is acceptable within 3% [21].

In Vivo

RT-Gel® is better tolerated and experienced by patients than standard of care for the prevention and treatment of radiation dermatitis. It also demonstrates superiority over comparative care with regards to the objectively measured outcomes of "skin toxicity" during radiation treatment of patients receiving radical radiation therapy for head and neck or breast cancers, as observed in Fig 6 and 7. Fig 3 and 4 indicate patients' satisfaction rating with prevention of skin deterioration when treating with RT-Gel® vs standard of care and StrataXRT® respectively. Both graphs indicate a significant preference for treatment with RT-Gel®. This proves RT-Gel® superior compared to both the standard of care as well as when compared to treatment with StrataXRT®. RT-Gel® is thus accepted as the preferred treatment for the prevention of RD and the prevention of skin deterioration caused by radiation therapy.

This small study concludes that the topical device RT-Gel®, is effective and better preferred and tolerated than standard of care. It outperformed StrataXRT on both patient satisfaction scores and toxicity grading. The protective properties can be ascribed to the products ability to retain skin integrity during radiation treatment as described by Kumar et al. It retains moisture and reduces skin friability ensuring the protective barrier of the skin remains intact, reducing the inflammatory response.

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Declarations

Authors JR Snyman and I Laurens declare that they are shareholders in dermaV Pharmaceuticals Pty Ltd responsible for the development of RT Gel®, KR Snyman and I Oelofse declare no conflict of interest.

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