

An Innovative Complex of Benzene-Poly-Carboxylic Acid and Molybdenum, for Prevention and Treatment of Radiation Dermatitis

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Abstract

Radiation dermatitis occurs in up to 95 percent of patients receiving radiotherapy. The aim of this study was to evaluate whether topical application of a new Benzene-Poly-Carboxylic Acid and Molybdenum Complex (BP-C2) prophylactically could protect mice skin from irradiation-induced dermatitis or treat irradiation-induced skin dermatitis, when it already has occurred. The right posterior leg of male BALB/cfC3H mice was exposed to radiation dose of 30 Gy. For prevention studies, animals were treated with BP-C2 just prior to irradiation and three times a week for 5 weeks post-radiation. For treatment studies, animals were treated with BP-C2 three times a week for five weeks when skin injury was appeared following irradiation exposure. Animals were sacrificed and skin damage was assessed using a non-linear semi-quantitative scale, as well as histological studies. Acute skin dermatitis was observed in all control animals (n=8) following 30 Gy irradiation in form of edema and ulceration grade 4. No signs of skin dermatitis were observed in the irradiated area of animals (n=8) treated with BP-C2 prior to irradiation exposure. Moreover, treatment of injured animals with BP-C2 three times a week resulted in recovery of the skin and no erythema or ulceration was hereafter observed. BP-C2 represents a potentially promising agent for prevention and treatment of irradiation-induced skin dermatitis.

Keywords: BP-C2; Skin dermatitis; Electron beam irradiation; Prevention; Treatment

Abbreviations: BP-C2: Benzene-Poly-Carboxylic Acid and Molybdenum Complex; IVCs: Individually ventilated cages; SPF: In a specific pathogen free; H&E: Hematoxylin and Eosin; TGF- β : Tumor Growth Factor; IMRT: Introduction to the Intensity-modulated Radiation Therapy; 3D-CRT: Conformal Radiation Therapy

Introduction

Irradiation dermatitis occurs in up to 95 percent of cancer patients receiving radiotherapy, especially in patients with breast cancer, head and neck cancer, lung cancer, or sarcoma due to a higher radiation dose to the skin [1-7]. In most cases, the skin reaction is mild or moderate. Approximately 20 to 25 percent of patients experience moist desquamation and ulceration [8-10]. Irradiation-induced dermatitis has a profound impact on the quality of a patient's life, due to pain, discomfort and premature interruption of radiation therapy, resulting in inadequate cancer treatment. Irradiation-induced fibrosis may cause both cosmetic and functional impairment, which can lead to death or significant deterioration in quality of life. Different areas of the body have different sensitivities to radiation dermatitis. The most sensitive regions of the body are the anterior of the neck, extremities, chest, abdomen, and face [3].

The National Cancer Institute (NCI) in United States has developed a 4 stage criteria for classification of acute radiation dermatitis: a) Grade I – Faint erythema or desquamation, b) grade II – Moderate to brisk erythema or patchy, moist desquamation confined to skin folds and creases. Moderate swelling, c) grade III – Confluent, moist desquamation greater than 1.5 cm diameter, which is not confined to the skin folds. Pitting edema (severe swelling), and d) grade IV – Skin necrosis or ulceration of full thickness dermis (middle layer of skin) [2,11,12].

It is well known especially from the Russian literature that a complex of organic compounds with variable-valence metals, especially platinum and manganese, and molybdenum has radio-protective

properties [13]. BP-C2 is a complex of BP-Cx-1 and molybdenum. BP-Cx-1 is a complex of benzene-polycarboxylic acids and it is known for its detoxifying free-radical, anti-oxidant and anticancer activities [14,15]. Intra-gastric application of BP-C2 was performed in CBA mice and Wistar rats. Repeated intra-gastric administration of BP-C2 promoted radioprotection against radiation doses in the median lethal dose range. The optimal radio-protective doses were 81.0 mg/kg BW for mice and 93.7 mg/kg BW for rats [13]. No topical application of BP-C2 was used. The conclusion was that the use of BP-C2 promotes a favorable course and increases the likelihood of a favorable outcome of acute irradiation injury. The available Russian literature suggest promising area of research, namely creating effective anti-radiation pharmacological means for medical protection with characteristics that meet the current high standards for effectiveness and convenience are complexes of organic compounds and variable-valence metals [13]. On the base of these facts, the present study aims to test the potential of BP-C2, an innovative molecule, on prevention and treatment of radiation-induced skin dermatitis using a mice model.

Experimental Methods

Chemical and biological reagents

BP-C2 (Figure 1) was kindly supplied by Meabco Oncology

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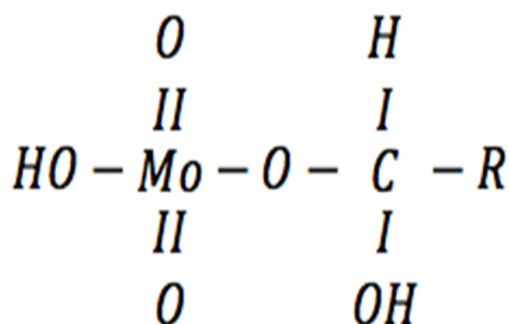


Figure 1: Chemical structure of BP-C2 analog. R- fragment of the ligand with molecular weight of 475 Da.

A/S, Copenhagen, Denmark. The synthesis of BP-C2 solution was done in a single step starting from hydrolyzed humic acid (BP-Cx-1 ligand) and ammonium molybdate tetrahydrate (Brutto formula: $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, MM 1235g/mol) in water in presence of 10% aq ammonia under ultrasound treatment at 22.0 kHz for ten minutes. The ligand, BP-Cx-1, is a polymer of benzene poly-carboxylic acids, obtained by alkaline oxidation from hydrolyzed lignin. All other chemicals were purchased from Sigma (Saint Louis, MO, USA) or other local sources. LD₅₀ of BP-C2 is 8000 mg/kg. Composition of 1 ml of the trial medication BP-C2 is 1.5 mg of the amount of molybdenum-ammonium salts of benzene -poly-carbonic acids, including 0.2 mg of Molybdenum.

Animals

Male BALB/cfC3H mice, 5 weeks old; 18-20 g body weights were purchased from Harlan Laboratories Jerusalem, Israel. Experiments were performed with 8 mice in each group. The animal protocols used in this work were evaluated and approved by the Ethics Commission on Animal Use (CEUA) of the Technion-Israel Institute of Technology. They are in accordance with FELASA guidelines and the National law for Laboratory Animal Experimentation (Law no. 18.611).

All mice were held in individually ventilated cages (IVCs) in a specific pathogen free (SPF) barrier unit with 5 mice in each cage. There was a constant room temperature of 20°C and a mean humidity of 55%. The animals received 2018 extruded rodent diet (Harlan Laboratories) and sterile acidified water (ad libitum) from time of arrival and throughout the study.

Radiation treatment

6 MeV electron beam from a medical linear accelerator (ELEKTA AB, Stockholm, Sweden) was used for irradiation. In order to facilitate local irradiation, a special cut-out insert with a circular 2 cm diameter aperture was prepared. A 0.5 cm tissue equivalent bolus was used to bring the maximal dose to the skin surface. The radiation output in the center of the aperture was measured with an ionization chamber. Mice were shaved in the leg side and anesthetized with an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (8 mg/kg). After 10 minutes, the right posterior leg of the animals was irradiated with a total dose of 30 Gy as described before [16]. 30 Gy was given in row of 5 times 6 GY/time. Histological findings of radiation-induced dermatitis were determined as described previously [17].

Treatment with BP-C2

For prevention studies, 5 weeks old animals were divided into two

groups; control and treated. Prior to irradiation exposure the treated group, animals were treated with BP-C2 and 3 times a week after irradiation for 10 weeks (Figure 2). For treatment studies, animals were irradiated with 30 Gy, and after 5 weeks when skin injury was observed animals were treated 3 times a week with BP-C2 for 5 weeks (Figure 3). At the end of the experiments, animals were sacrificed and uniformed taken skin biopsies were prepared for histopathological studies. The vehicle is physiologic saline and the control group consists of animals sprayed with physiologic saline, i.e., the saline treated group is a proper control group treated with the vehicle.

Skin effects

Following irradiation mice were thoroughly inspected several times per week and the quality of the skin was recorded by an independent pathologist. For monitoring the radiation dermatitis, photographs of the animals were taken twice a week and the skin injury score was assessed as follows: (0) normal, (1) erythema, (2) dry desquamation, (3) wet desquamation, and (4) ulceration. Skin damage was assessed using a non-linear semi-quantitative scale and by conventional histopathology. Skin damage was measured several times per week for 10 weeks.

Hematoxylin and eosin staining protocol

All histopathological procures were carried out at the Department of Pathology, Carmel Medical Center, Haifa, Israel, Paraffin sections were de-waxed in xylene and rehydrated through a series of alcohol

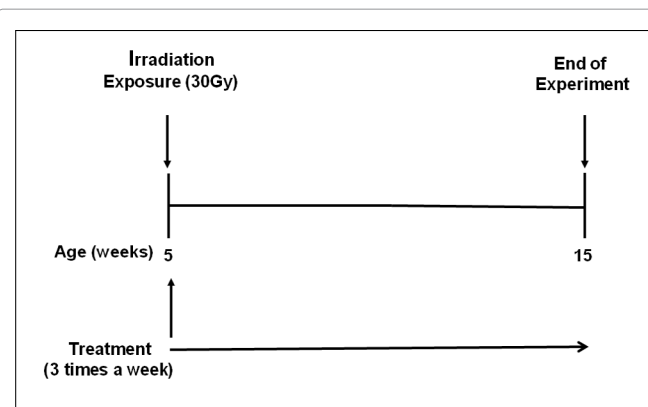


Figure 2: A schematic, prophylactic treatment regimen with BP-C2 of acute skin dermatitis in mice. For prevention studies, animals were treated with BP-C2 prior to irradiation exposure. After irradiation exposure to 30 Gy, animals were treated 3 times a week with BP-C2 for 10 weeks.

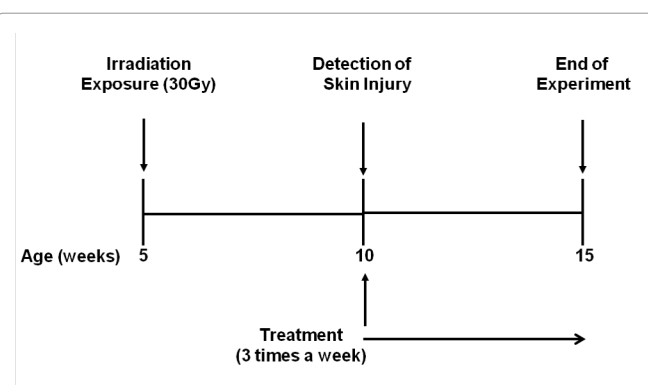


Figure 3: A schematic treatment regimen with BP-C2 after occurrence of acute skin dermatitis. Animals were exposed to irradiation, 30 Gy, and after 5 weeks when skin injury was observed, animals were treated 3 times a week with BP-C2 for 5 weeks.

to water using a Leica Autostainer XL ST5010. Once they were rehydrated, the slides were immersed in Gill's 2 Hematoxylin (Thermo-Fischer 6765007, Thermo-Fischer Scientific, Bishop Meadow Fischer, Loughborough, UK) for 1 minute, rinsed in running water for 1 minute, dipped in alkaline water, and then rinsed before being immersed in Eosin (Thermo-Fischer 6765009) for 1 minute. Sections were then rinsed in water, dehydrated and cleared in xylene using the Leica Autostainer XL before being permanently mounted.

Statistics

Contingency table analysis was used for statistical analysis. The main variable in this study was recorded on an ordinal 4-point fixed scale. The recommended model for performance of analysis of such variables is Contingency Table Analysis as performed. Analysis of Variance (ANOVA) demands continuously and normal distribution $N(\mu; \sigma)$ and even Dunn's model of ANOVA on Ranks will lose power with an outcome space including max 4 outcome. The tie configuration will destroy the power of a model and will obviously weaker compare to Contingency Table Analysis. $P < 0.05$ was considered significant.

Results

Prophylactic studies

In order to test the efficacy of BP-C2 on prevention of radiation induced skin injury, animals were treated with BP-C2 before radiation exposure and 3 times a week for more 10 weeks (Figure 2). The results indicated that acute skin reactions were observed in all control animals (8 animals/group) following 30 Gy of irradiation. The irradiated areas demonstrated dermatitis edema and ulceration grade IV. Interestingly, no skin dermatitis was observed in the irradiated area of animals the prophylactically treated with BP-C2, ($p < 0.01$) between the two groups. Representative macroscopic comparison of untreated control and treated animals with BP-C2 before and 3 times a week after irradiation are shown in Figure 4.

Treatment studies

In order to test the efficacy of BP-C2 on the treatment of radiation induced skin injury, animals that were injured by radiation exposure were treated 3 times a week for 5 weeks (Figure 3). The results indicate that all control animals (8 animals/group) were developed breakdown of the epidermal barrier and ulcerations grade IV after exposure to 30 Gy. Treatment of injured animals (8 animals/group) with BP-C2, 3 times a week for 5 weeks resulted in recovery of the skin and

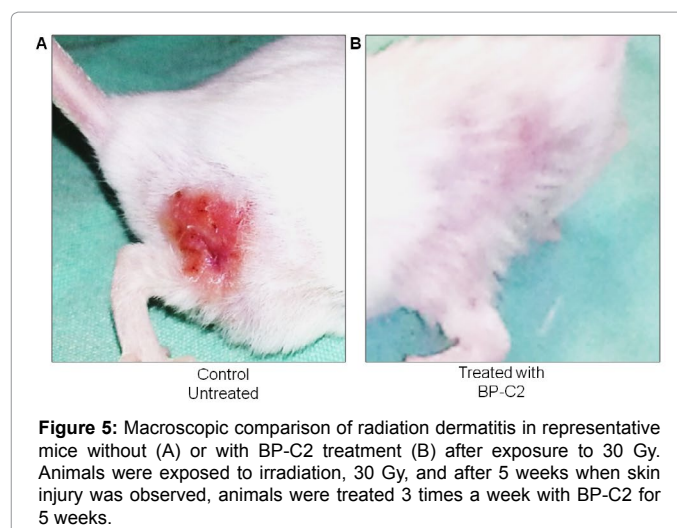
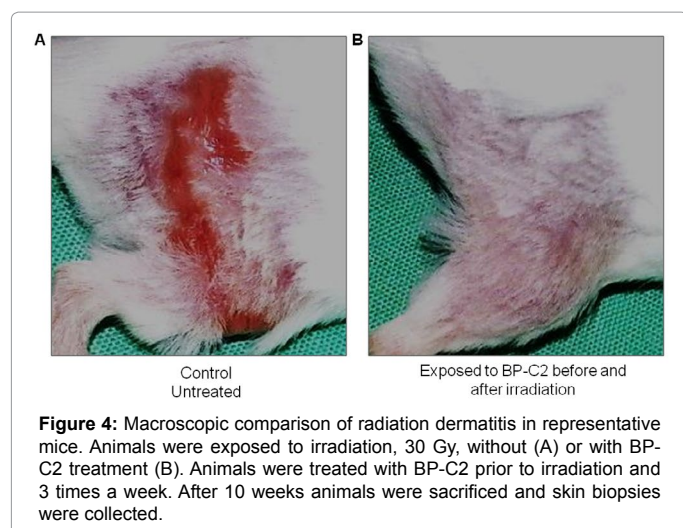
no erythema or ulceration were observed ($p < 0.001$). Representative macroscopic comparison of control and treated animals are shown in Figure 5. The results indicated that BP-C2 treatment recovered the skin injury induced by irradiation.

Histopathological studies

For histological evaluation of skin biopsies from control and treated animals, skin biopsies were fixed in formalin and paraffin blocks were prepared. Four micron sections were prepared, stained with hematoxylin and eosin (H&E) and examined as described under "Methods and Materials". Ten weeks post-irradiation skin tissue shows severe irradiation injury results with complete loss of the epidermis and persistent fibrin exudates, edema and ulceration covered by fibrin-inflammatory debris grade IV (Figure 6A). However, in skin biopsied from treated animals with BP-C2 prior to irradiation exposure and 3 times a week for 10 weeks, a mild injury in the hair roots was observed and scattered melanin granules were present within the hair and hair roots (Figure 6B). Five weeks post irradiation skin biopsies from representative animals show loss of epidermis, edema and ulceration covered by fibrin-inflammatory debris grade IV (Figure 6C). On the other hand, treatment of the injured animals with BP-C2, 3 times a week for 5 weeks, showed recovery of skin tissue with atrophy of epidermal layers, dermal structures were presented without ulceration. In addition, hair follicles were present with scattered melanin granules however, very mild edema and fibrosis was detected in the superficial dermis with mild chronic inflammation (Figure 6D).

Discussion

The present study has shown that topical application of BP-C2 protects against irradiation-induced dermatitis in mice whether BP-C2 is used prophylactically or as a treatment after skin dermatitis has occurred. We have demonstrated that when BP-C2 is used prophylactically no signs of skin dermatitis can be observed. When skin ulcers have occurred after irradiation they disappear completely after topical application of BP-C2; this is confirmed macroscopically as well as by histopathological examinations. Histopathological examination demonstrated almost normal skin biopsies after treatment with BP-C2 without ulceration but with mild edema, mild fibrosis, and mild chronic inflammation. The effect on skin ulcers together with non-toxicity or side effects, makes BP-C2 a promising drug for treatment of radiotherapy induced skin dermatitis. Skin dermatitis is not only seen after radiotherapy for cancer but also as a complication to post-radiation exposure from accidents or weapons, such as "dirty bomb" [6]. The



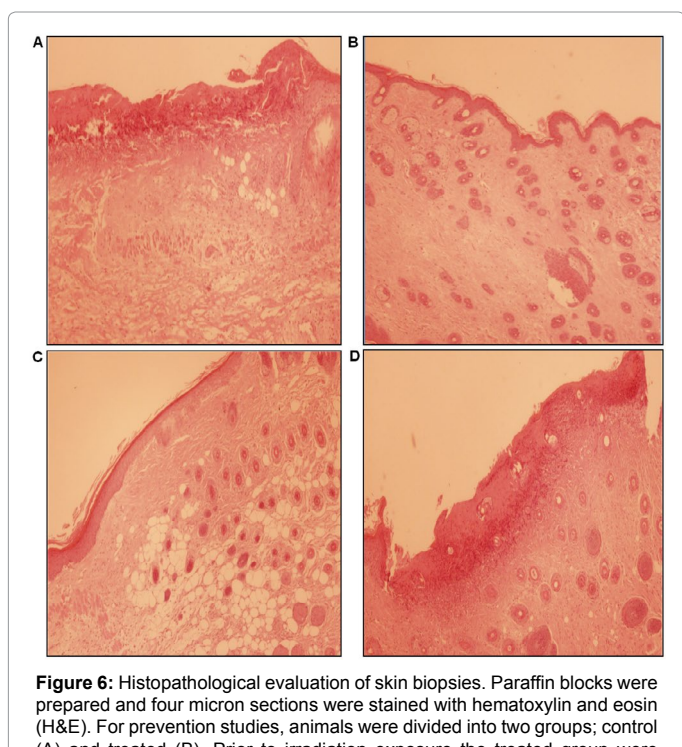


Figure 6: Histopathological evaluation of skin biopsies. Paraffin blocks were prepared and four micron sections were stained with hematoxylin and eosin (H&E). For prevention studies, animals were divided into two groups; control (A) and treated (B). Prior to irradiation exposure the treated group were treated with BP-C2 followed by treatment 3 times a week after irradiation for 10 weeks (B). For treatment studies, animals were irradiated with 30 Gy, and after 5 weeks when skin injury was observed animals were treated 3 times a week with BP-C2 for 5 weeks (D) and compare to untreated animals (C). In the superficial dermis of untreated animals (A and C), edema, fibrosis and chronic inflammation were detected. On the other hand, treatment with BP-C2 irradiation exposure showed intact epidermal barrier with very little edema, very mild fibrosis and very mild chronic inflammation without ulceration (B and C).

irradiation-induced toxicity such as skin dermatitis can result in poor outcome due to interrupted or limited radiotherapy adversely affecting quality of life [18]. Therefore, it is of utmost importance to develop nontoxic anti-skin dermatitis treatment to be used during radiotherapy without impairing the antitumor efficacy of the irradiation.

The Danish pharmaceutical company Meabco A/S has recently developed a new substance based on the BP-C2, a novel complex of benzene-poly-carboxylic acids with a very low concentration of molybdenum, which from a theoretical point of view should have a strong impact on irradiation-induced dermatitis and on healing of irradiated-induced skin dermatitis. So far we have shown *in vitro* and in *in vivo* experiments that BP-C2 is a strong modulator of the innate immune system and that it corrects hematological abnormalities such as anemia, thrombocytopenia and neutropenia often seen in patients with cancer [19]. Other mechanisms of action (MoA) involved could be DNA damage and improve DNA repair after irradiation, the presence of the so-called membranotropic effect and effects on various genes and cytokines [20].

Radiotherapy induced skin dermatitis exists in an acute and a chronic form [21,22]. In this study we use a high single radiation dose of 30 Gy in order to cause severe skin dermatitis. It is well known, that repeated low doses of ionizing radiation causes chronic skin dermatitis. It is also known, that AP-1 transcription factor is activated by irradiation and that this activation causes induction of Tumor Growth Factor (TGF- β) in the skin and that this TGF- β is partly responsible for radiation-induced fibrosis [23]. We are currently investigating the

potential altered immune cell proportions in irradiation-induced skin dermatitis in mice.

Acute injury, which occurs within hours to weeks after radiation exposure, results from immediate structural tissue damage, generation of short-lived free radicals [24], irreversible double-stranded breaks in nuclear and mitochondrial DNA, and initiation of an inflammatory response in the epidermis and dermis [18-21]. Repeated exposure to low-dose ionizing radiation does not allow time for cells to repair DNA or tissue damage. The accumulation of radiation-induced changes to dermal vasculature, appendage structures, and epidermal stem cells results in progression of irradiation dermatitis through characteristic stages of severity.

Irradiation-induced dermatitis represents one of the most important dose limiting factors in radiotherapy [21,22]. In the present study we are focusing on the acute form of radiotherapy induced skin dermatitis, which normally develops within a few weeks after exposure to a high dose of ionizing radiation. The skin dermatitis shows erythema, epiling, dry- and moist-desquamation and erosion/ulceration. In current studies in mice we are looking into the occurrence of chronic dermatitis. In a recent study the outcome and toxicity of patients with anal cancer undergoing Intensity-modulated Radiation Therapy, IMRT, or Conformal Radiation Therapy (3D-CRT) was evaluated. The study demonstrated that IMRT could reduce severe acute skin toxicity significantly ($p < 0.001$) compared to 3D-CRT. No toxicity grade 4 was observed and G2/3 toxicity was reduced from 94.6% to 63.2% [25]. No effect on overall survival, progression-free survival or on local control was observed. Irradiation given in a single high dose or in sub-erythelial doses for 14 days have been demonstrated to exert negative effects on the epidermal barrier, leading to barrier disruption [24]. In contrast, low doses of irradiation exert positive effects on the epidermal barrier, without clinically evident inflammation or barrier disruption. The aim of our study was to see whether a newly developed anti irradiation drug could prevent stage IV skin dermatitis. That is why we used irradiation with a single high dose of 30 Gy in order to demonstrate negative effects of irradiation on the epidermal barrier. In a recent study promising results were published with treatment of a Toll-like receptor 5 agonist. The agonist reduced irradiation induced skin dermatitis associated with epidermal hyperplasia and dermal inflammation through activation of endogenous antioxidants reducing free radicals [26].

Currently, no effective treatment exists to prevent or treat skin dermatitis in humans. Therefore, there is a huge unmet clinical need to develop new effective treatments of radiation induced skin dermatitis. The promising results with BP-C2 in the present study makes hope for future treatments of radiotherapy-induced skin dermatitis. Current studies will hopefully demonstrate the effect of BP-C2 on chronic skin dermatitis i.e., the manifestation of fibrosis-related irradiation-induced dermatitis and the potential genetic background. We are now waiting for the additional studies on the predictive ability of synergistically acting genes, both in tissues and in peripheral blood, which probably will increase our knowledge further on the mechanism behind acute as well as chronic skin dermatitis after irradiation.

Overall, many trials have been conducted to evaluate a large variety of products and methods in prevention of acute radiation-induced skin dermatitis. However, they do not support a general consensus on a superior product that should be used in this setting. Concerning treatments assessed for the management of radiation-induced skin reactions include topical steroid creams [27], non-steroidal creams [17,28] and herbal remedies [29,30]. Bordelaya et al. have recently demonstrated that toll-like 5 agonist protects mice from dermatitis and oral mucositis caused by local radiation of head and neck cancer [26].

The small number and large variety of trials make it difficult to draw any conclusions concerning the management of radiation induced skin dermatitis. Thus trials assessing products used for prevention of acute induced skin injuries as well as treatments for radiation-induced skin reactions, especially moist desquamation and ulceration reactions (grades III and IV), are needed.

Conclusion

In summary, the present study has shown that topical application of a novel Complex of Benzene-Poly-Carboxylic Acid and Molybdenum (BP-C2) protects against irradiation-induced dermatitis whether BP-C2 is used prophylactically. Moreover, when skin ulcers have occurred after irradiation it can be cured completely after topical application of BP-C2. These results may indicate that BP-C2 can be used for prevention and treatment of skin injury following irradiation exposure.

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