Treatment and Follow-up of Patients Suffering from the Cutaneous Radiation Syndrome

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Abstract

The hazards of acute radiation exposure are commonly addressed with respect to total body gamma or neutron irradiation, resulting primarily in bone marrow failure as the main clinically relevant aspect of the acute radiation disease. Under conditions of inhomogeneous exposure, as they are characteristic for many accident scenarios, other organ systems, such as the skin may become more important in determining clinical prognosis. This became especially obvious in the two worst radiation accidents since 1945, the Chernobyl accident in April 1986 and the Goiania accident in September 1987.

The characteristic chronic sequelae of accidental cutaneous radiation exposure and therapeutic results have been described based on own clinical experience with treating patients with acute and late cutaneous effects after therapeutic irradiation, and a distinct group of patients having survived the Chernobyl nuclear power plant accident of April 26, 1986.

Apart from clinical examination, histological analysis and high-frequency (20MHz) ultrasound as well as a variety of functional tests have been used to determine the extent of radiation fibrosis and to exclude malignant transformation of keratoses and ulcers.

Treatment included, apart from dermatosurgical procedures and plastic surgery for disabling contractures or ulcers, argon laser treatment of telangiectasias, topical tretinoin 0,005% (Epi-Aberel®, Cilag, Frankfurt), etretinate and acitretin (TigasonR, Hoffmann LaRoche, Grenzach) for radiation keratoses, partly combined with a novel, nonatrophogenic steroid, Mometasonefuroate (EloconR, Schering-Plough, New Jersey) to antagonize inflammatory reactions, and low-dose interferon-gamma (PolyferonR, Rentschler, Laupheim) for extensive radiation fibrosis. Basic dermatotherapy was performed with an ointment containing linoleic acid (LinolaR, Wolff, Bielefeld). With this combination treatment, transepidermal water loss could be sustained, progression of keratoses and inflammation were stopped. The most remarkable result was the reduction of radiation fibrosis: sonographically determined skin thickness partly returned to normal levels after treatment of 18 months with Interferon gamma 50ug s.c. 3x/week. Based upon therapeutic experience with patients undergoing radiation therapy, symptomatic relief of pruritus can be achieved by administration of nonsedating antihistamines, such as Loratadine. In the chronic stage of the CRS after radiation therapy, where interferon gamma cannot be used, reduction of radiation-induced cutaneous fibrosis can be reached by a combination of Vitamin E and pentoxifylline even two decades after radiation exposure. It is concluded that under accidental partial body exposure with high doses of beta and gamma irradiation, the predominant involvement of the skin, described as the cutaneous radiation syndrome, may become the characteristic trait of this increasingly probable accident pattern. Though treatment is complex and requires dermatologic and radiobiological expertise, it results in marked clinical improvement of the affected patients. These results demonstrate that considerable progress has been achieved during the last years regarding diagnosis and treatment of cutaneous radiation sequelae. Surgery has to be considered the treatment of choice for radiation carcinoma, but is no longer the only available therapeutic option. However, systematic controlled clinical trials are still missing for these options.

Introduction

As radiation accidents basically are very rare incidents, standardization of treatment is difficult to achieve. Additionally, the effects of ionizing radiation on skin have long been neglected in defining guidelines for treatment and follow-up. Therefore, the status of treatment of
cutaneous radiation sequelae apart from surgical methods is so far not satisfactory (1,2). An established treatment scheme which would go beyond recommendations, based on anecdotal observations, does not exist.

Additionally, differing procedures in documentation of accidents further worsen the intercomparability of therapeutic efforts in accident situations which generally are separated by large gaps in space and time. This situation may improve after implementation of appropriate data base systems (3) where all radiation accidents can be reported to.

Generally, the clinical course of cutaneous radiation reactions follows a distinct clinical pattern, for which the term „cutaneous radiation syndrome“ (CRS) has been coined (4). Within minutes to hours after exposure an erythematous reaction develops, which may be associated with a burning itch. This prodromal stage is transient in nature, and is followed after upto 36 hrs by a clinically inapparent latency stage. The manifestational stage is characterized by occurrence of an intensively erythematous skin which may show some scaling. In more severe conditions subepidermal blisters and even ulcerations may develop. Though resembling skin lesions produced by thermal injury, the time course and underlying processes involved in the development of the CRS are so different from thermal burns (5), that the terms „radiation burns“ or „β-burns“ are considered inappropriate for this clinical condition and misleading and should therefore be abandoned.

In the chronic stage of the CRS three clinical symptoms are dominating the further course:
- radiation keratoses may develop in all exposed areas. They have to be considered precancerous lesions and should be monitored thoroughly.
- radiation fibrosis is caused by an increase of collagenous tissue in dermal and subcutaneous fibroblasts which may lead to pseudoatrophy of fatty tissue. Fibrosis may lead to an occlusion of blood vessels and can thus cause secondary ulceration.
- telangiectasias are a characteristic sign of the chronic stage of the CRS in humans (they may be absent in many laboratory animals, among them pigs). Apart from cosmetic disfiguring, they may cause a permanent itching sensation and a feeling of warmness, which is reported to be disturbing by the affected patients.

Treatment of the CRS and Discussion

Treatment has to focus on symptomatic relief and the avoidance of additional risk to the patients. The applied therapies, dosages, numbers of patients to which the treatment had been applied and the therapeutic outcome are summarized in table 1.

With regard to the manifestational stage of CRS our experience is limited to radiotherapy patients. In these conditions, an erythematous and erosive condition occasionally occurs, which is associated often with a burning itch. Treatment with loratadine, a non-sedating and mast-cell stabilizing antihistamine, induced a marked relief of these symptoms and a shortening of the erythematous phase as compared to untreated patients (Peter et al., submitted). Topical steroids generally can be used with good success, as reported earlier by other authors (6).

Topical dressings of Tetrachlorodekaoxide (TCDO) induce considerable granulation and reepithelization in erosive skin conditions (Braun-Falco and Landthaler, unpublished observations). These data confirm the radioprotective properties of TCDO reported by other authors in irradiated mice (7), rats (8) and regenerative capacities in complicated wounds (9).

Additional treatment modalities which have been reported to be of value in the manifestational stage are cleansing of the oral cavity and administration of pilocarpine for prevention of mucositis (10, 11) as well as heparinization and antibiotic prophylaxis for bacterial and viral infections (1).
In some older studies beneficial effects of hydroxyethylrutosides (12) and bovine blood extracts (13) on radiation-induced acute skin reactions have been reported. It should be noted, however, that these reports have been based on animal experiments or on open trials with comparatively small patient groups, respectively.

Our therapeutic experience with the chronic stage of the CRS comes, apart from the survivors of the Chernobyl accident, from patients suffering from chronic cutaneous sequelae following therapeutic irradiation. These experiences shall be discussed consecutively. All Chernobyl patients who have been treated by us responded well to a basic therapy with a specific ointment containing linoleic acid (Linola Fett®, Wolff, Bielefeld), which led to a marked decrease of the initially severely increased transepidermal water loss, as determined by evaporimetry. In the meantime, this beneficial effect of linoleic acids has been demonstrated in animal experiments as well (14). Teleangiectasias, though primarily a cosmetical problem, in some localizations, such as the ankles of the knees, caused discomfort due to sensations of a burning itch and heat, which disappeared after treatment of telangiectasias by Argon laser.

Tretinoin cream 0.005% (Epi Aberel®, Cilag, Frankfurt), applied once daily, led to clearance of focal and patchy radiation keratoses, as it has been reported for solar keratoses (15). In more extensive lesions, oral application of the retinoid Acitretin (0,1-0,2 mg/kg/d) was used, analogous to the reported treatment of radiation-induced keratoacanthomas (16). However, on radiation-exposed skin tretinoin cream appeared to be more irritant than it is known from patients with actinic keratoses; therefore, intermittent antiinflammatory treatment with topical steroids was necessary. To avoid additional damage of the atrophic skin caused by steroid atrophy, a novel steroid preparation, which has been proven to be nonatrophogenic in a variety of clinical trials (Mometasone furoate, Elocon®, Schering-Plough, New Jersey), was applied intermittently.

The most striking results were reached with subcutaneous administration of interferon (IFN) gamma (Polyferon®, Rentschler, Laupheim), in eight patients with severe and extensive radiation fibrosis: in six patients receiving IFN gamma for 18 months in a dosage of 50 µg s.c. 3x/week according to a protocol used in scleroderma patients (17) fibrosis could be reduced almost to the level of uninvolved contralateral skin, as determined by cutaneous 20 MHz sonography (cp. also the article of P. Gottlober et al, this issue). Side effects which were noted included elevation of body temperature up to 38.5°C after the first two injections, and a reduced frequency of herpesvirus infections, which recurred in three patients after discontinuation of interferon treatment. In two patients who rejected interferon injections after the first injection, and who were followed up together with the other six patients, an increase of fibrosis occurred during the observation period.

The efficacy of IFN gamma in radiation fibrosis may be explained in part by its antagonizing effect towards the cytokine TGF-beta, which is of eminent importance for the induction of radiation fibrosis (18). Another therapeutic option for radiation fibrosis is the combined administration of Pentoxyfilline (PTX) 3x400 mg/d and Vitamin E 1x400 mg/d. By this regimen, applied for a minimum of six months, radiation fibrosis persisting and being progressive for more than 20 years could be reduced (19). Controversial data exist in the literature for superoxide dismutase with regard to its efficacy in reducing acute radiation-induced tissue reactions. In muscular and subcutaneous fibrosis however, there is good evidence of a beneficial effect (20). Surgical procedures followed in general reported guidelines (21) and included excision of ulcers and contractures; wound closure was performed with split and full thickness skin grafts, on certain instances vascularized flaps were used. All grafts healed without complications, even in localizations where the surrounding tissue was affected by late radiation effects. This is a specifically interesting aspect of the CRS in the Chernobyl survivors, as due to
the primary cause of cutaneous lesions, namely short-range nuclides causing cutaneous contamination, only the upper parts of the dermis and subcutis were affected, whereas the larger vessels penetrating the muscle fascia were not or only partially harmed. Therefore the surgical experience derived from patients with skin fibrosis after deeply penetrating radiation therapy, that skin grafts do not heal if not the complete surrounding affected tissue is removed, proved to be inadequate for the survivors of the Chernobyl accident.

In conclusion it can be stated that the last decade not only brought a substantial gain in understanding about the mechanisms underlying cutaneous radiation reactions, but this knowledge could also be transformed into several novel therapeutic approaches for the benefit of those patients who suffered so badly from the most severe accident in the history of the civilian use of nuclear energy so far.

References


### Table 1 Symptom-oriented treatment of the Cutaneous Radiation Syndrome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
<th>Application</th>
<th>Dosage</th>
<th>Result</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>Antihistamines</td>
<td>p.o.</td>
<td>10mg q.d.</td>
<td>relief of itch</td>
<td>-</td>
</tr>
<tr>
<td>Erythema</td>
<td>Steroids</td>
<td>topical b.i.d.</td>
<td></td>
<td>alleviation</td>
<td>none if used less than 3 wks</td>
</tr>
<tr>
<td>Blisters</td>
<td>Steroids</td>
<td>wet dressing</td>
<td>t.i.d.</td>
<td>alleviation</td>
<td>-</td>
</tr>
<tr>
<td>Dryness</td>
<td>Linoleic</td>
<td>topical 1 x /day</td>
<td></td>
<td>inhibition of water loss</td>
<td>-</td>
</tr>
<tr>
<td>Keratoses</td>
<td>Tretinoin</td>
<td>topical</td>
<td>1 x /day</td>
<td>clearance</td>
<td>irritation dryness of lips</td>
</tr>
<tr>
<td></td>
<td>Acitretin</td>
<td>oral</td>
<td>0.1-0.3 mg/kg</td>
<td>moderate</td>
<td>-</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Mometasone</td>
<td>topical</td>
<td>3-4 x /week</td>
<td>alleviation</td>
<td>Fever</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>IFN gamma</td>
<td>s.c.</td>
<td>50 μg 3x/w</td>
<td>reduction</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>PTX+Vit E</td>
<td>p.o.</td>
<td>400mg t.i.d.</td>
<td>reduction</td>
<td>Fever</td>
</tr>
</tbody>
</table>

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