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Amelioration of the pathological changes induced by radiotherapy in normal tissues

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Abstract

Damage to normal tissues remains the most important limiting factor in the treatment of cancer by radiotherapy. In order to deliver a radiation dose sufficient to eradicate a localised tumour, the normal tissues need to be protected. A number of pharmacological agents have been used experimentally, and some clinically, to alleviate radiation damage to normal tissues but at present there is no effective clinical treatment to protect normal tissues against radiation injury. This paper reviews the efficacy of pharmacological substances used after radiation exposure. The limited evidence available suggests that radiation insult, like many other tissue injuries, is amenable to pharmacological intervention. However, care must be taken in the administration of these substances for the management of different aspects of radiation damage because there appears to be a tissue-specific response to different pharmacological agents. Also, one must be aware of the limitations of results obtained from animal models, which do not necessarily correlate to benefits in the clinic; the conflicting results reported with some modifiers of radiation damage; and the toxicity of these substances and radiation doses used in published studies. Conflicting results may arise from differences in the pathophysiologic processes involved in the development of radiation lesions in different tissues, and in the markers used to assess the efficacy of treatment agents.

Introduction

Radiotherapy is one of the main modalities for the treatment of cancer. More than 50% of all cancer patients in the Western world receive radiotherapy during the course of treatment, and, undoubtedly, radiotherapy will remain a treatment of choice for the foreseeable future. In the radiotherapy of localised tumours it must be possible, at least theoretically, to eradicate the tumour if a large enough dose of radiation can be delivered. However, practically, there is always the danger of damaging normal tissues adjacent to the tumour. The risk of damage to normal tissues increases with the radiation dose, as does the probability of local tumour control. Therefore, the most effective radiation dose delivered to the patient will always be limited by the risk of damaging normal tissues within the treatment field and those surrounding the tumour. Factors such as the total radiation dose, overall treatment time, dose per fraction, dose rate and radiation quality have been examined, and a number of protocols have been developed in order to improve the therapeutic ratio in radiotherapy. The majority of these protocols have concentrated on optimising dose fractionation schedules. Recently, the therapeutic ratio has been further improved by using multiple field treatment and intensity-modulated radiation therapy. However, even with the best available treatment planning, normal tissues within the path of radiation and surrounding the tumour will be involved in the target volume. Damage to normal tissues remains the most important limiting factor in radiotherapy. In order to deliver a sufficient radiation dose to successfully eradicate a localised tumour, the normal tissue should be protected.

Radiation injury to normal tissues is non-specific and generally produces no pathognomonic morphological changes. Radiation damage is characterised by alterations in the structure of parenchyma and supportive tissues, the severity of which depends on the tissue and the dose of radiation. A number of agents have been used experimentally, and some clinically, to alleviate radiation damage but at present there is no effective clinical treatment to protect against radiation injury, although some symptoms such as swelling or pain during the inflammatory phase may respond to corticosteroids (Godwin-Austin et al 1975).

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This paper reviews the the efficacy of pharmacological substances used after radiation exposure. Classic radioprotectors – substances that must be administered before and be present at the time of irradiation, such as amifostine (Brizel et al 2000; Vujaskovic et al 2002) are not included.

Stem cell therapy shows promise in the treatment of radiation damage (Rezvani et al 2001; Bertho et al 2002; Chapel et al 2003; Lombaert et al 2006) but is not reviewed here.

Experimental studies

Steroids

Steroids were possibly the first group of drugs used in the treatment of radiation lesions. Early work mainly used steroids to alleviate acute inflammatory reactions. After an unsuccessful attempt by Smith et al (1950), Marshall (1953) demonstrated a beneficial effect of cortisone treatment (0.25 mg daily) starting 7 days after irradiation of mouse skin with single X-ray doses of approximately 35 or 40 Gy. This treatment had no effect on the incidence of moist desquamation but significantly delayed its development in animals treated with cortisone compared with animals treated with radiation only. Average delay in the development of lesion was about 7 days. Later, complete resolution of neurological deficit resulting from delayed cerebral radiation necrosis was reported after corticosteroid therapy (Martins et al 1977; Shaw & Bates 1984). This was followed by reports that steroids protected irradiated rat lung from early interstitial oedema, delayed alveolitis without reducing its severity, significantly reduced the alveolar protein leak (Ward et al 1993) and alleviated the reduction in total lung compliance in rats within 1 month of therapy (Moss et al 1960). However, steroid treatment had no beneficial effect on the development of late fibrosis (Ward et al 1993).

Methylprednisolone administered i.p. alleviated interstitial oedema of the lung, delayed alveolitis and reduced leakiness of the lung after bilateral irradiation in rats (Ward et al 1993). Steroids also reduced the severity of inflammation when administered throughout the period of alveolitis. Prednisolone administered just before and just after irradiation, or after the development of radiation pnueomonitis, significantly reduced pulmonary lethality in mice given total body irradiation (TBI) (Phillips et al 1975). However, death occurred rapidly when the drug was stopped. Although Brown (1956) observed remarkable modification in the response of rat lung to approximately 3 Gy of X-rays with cortisone treatment, overall he concluded that cortisone alone or in combination with terramycin neither increased nor decreased survival of animals after thoracic irradiation. Fleming et al (1962) failed to modify the effects of irradiation on dog lung using cortisone. Jacob et al (1984) and Tada et al (1997) also reported that dexamethasone failed to improve the survival of whole-body-irradiated mice and necrosis of brain, respectively.

While low doses of prednisolone (18 mg kg^{-1} i.p.) showed some beneficial effect in reducing the combined action of cranial irradiation (10 Gy, single dose) and methotrexate in rats, larger doses of prednisolone (36 mg kg^{-1} i.p.) enhanced behavioural changes induced by a combination of radiation and methotrexate in young rats (Mullenix et al 1994).

Beneficial effects of steroidal anti-inflammatory drugs in reducing radiation-induced skin reactions were also reported in rabbits (Lefaix et al 1992). It was shown that intramuscular injection of betamethasone 24 h and 4 weeks after irradiation reduced moist desquamation of rabbit skin but had no beneficial effect on the development of late radiation-induced dermal necrosis. Results were the same when betamethasone was combined with dexchlorpheniramine. Betamethasone combined with the haemorheological agent trimetazidine was effective up to 4 weeks after irradiation. Dexamethasone (0.25 mg kg^{-1} daily) was reported to reduce vascular damage after X-ray irradiation of rabbit brain, monitored by vascular permeability (Blomstrand et al 1975).

Lurie & Casarett (1975) reported that adrenalectomy had a profound effect on the severity and progression of radiation-induced nephrosclerosis in rats. From comparison of their findings with those of Wachholz & Casarett (1970), these authors concluded that adrenalectomy accelerated the development of nephrosclerosis after renal irradiation. It was suggested that glucocorticoids and/or corticosterone protect the microvascular endothelium against excessive constrictive and permeability changes. Lack of adrenocorticoid in adrenalectomised rats has resulted in severe exacerbation of the permeability changes resulting from irradiation, therefore accelerating the development of radiation-induced nephrosclerosis.

However, steroid administration, even in small doses, adversely affected the survival of rabbits (Cladwell 1971) and rats (Berdjis 1960) after renal irradiation. Similarly, Stryker et al (1976) reported that prednisolone had no beneficial effect on radiation-induced acute inflammatory reaction of the rectum in dogs, and even increased the severity of the late tissue damage. Treatment with dexamethasone (2.9 mg kg^{-1} day^{-1} i.m.) did not improve the survival of Rhesus monkeys after brain irradiation (Martins et al 1977). No significant improvement with regard to the latency to onset or the incidence of neurological symptoms or severity of white-matter necrosis was found. The only difference was a delay of about 14 days in the development of scalp epilation with dexamethasone.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The NSAIDs are a chemically heterogenous group of drugs that have a common property of inhibiting cyclo-oxygenase activity (Higgs & Vane 1989). It is generally accepted that NSAIDs act by inhibiting the synthesis of stable prostaglandins from arachidonic acid (Vane 1971). However, the action of NSAIDs appears to be more complex than this, as these substances show other activities such as neutrophil activation and uncoupling of oxidative phosphorylation that do not depend on inhibition of prostaglandin synthesis (Kitsis et al 1991). Abramson & Weissmann (1989) have suggested that while inhibition of prostaglandin synthesis might be the mode of action of some NSAIDs, others may act by inserting into the lipid bilayer of the plasma membrane, and interfering with signalling and protein–protein interactions.

Indometacin is a potent inhibitor of prostaglandin synthesis. Treatment with indometacin and diclofenac sodium increased granulocyte counts in the blood of mice given sublethal doses of gamma irradiation (Pospisil et al 1986, 1989). However,

administration of sodium salicylate and indometacin together decreased the beneficial effects of indometacin. Rose et al (1992) reported reduced polymorphonuclear leucocyte infiltration and decreased tissue degeneration in indometacin-treated rats after 50 Gy (single dose) of whole-abdomen irradiation.

Indometacin has been shown to be beneficial in reducing the severity of radiation-induced oesophagitis in mice (Tochner et al 1990) and the opossum (Northway et al 1980).

In-vitro, indometacin stimulated the proliferation of murine haematopoietic stem cells (Estrov & Resnitzky 1983), and administration of indometacin after sub-lethal (4 Gy) TBI of mice induced a rapid recovery of all nucleated spleen cell populations (Serushago et al 1987). This might be due to the enhancement of cell mobilisation from bone marrow rather than proliferation of splenic cells. However, when prostaglandin E_2 (PGE_2) was administered together with indometacin, the recovery of splenic cells diminished to the level of controls. This suggests that the restoration of splenic cells by indometacin was probably due to a diminished level of prostaglandins in the plasma of irradiated mice.

By contrast, Hofer et al (1992) reported adverse reactions associated with the administration of indometacin or diclofenac after 10 Gy TBI in mice. Administration of indometacin (0.7–3.3 $mg\,kg^{-1}$ s.c.) or diclofenac (5 $mg\,kg^{-1}$ s.c.) 2 or 24 h after irradiation significantly reduced the survival of mice after TBI. All animals treated with indometacin or diclofenac died within 9 days after irradiation, whereas 50% of the animals in the radiation-only group survived to this time point. Severe enteropathy, manifest by swelling of the lamina propria, irregularities of the mucosal surface and cystic dilation of the crypts, was reported in these animals. Death was attributed to enhanced leakage of endotoxin from the intestine. It appears that prostaglandin synthesis inhibitors that have a beneficial effect after sub-lethal doses or local irradiation of skin can have adverse reactions after lethal doses or irradiation of other organs. Care must be taken in the administration of these substances for the management of different aspects of radiation damage (Hofer et al 1992). Northway et al (1988) tested a number of NSAIDs, including aspirin and piroxicam, at several doses and via different routes of administration, all starting before start of radiotherapy and continuing for about 1 week afterwards, but did not observe any beneficial effect in development of radiation proctitis induced by a 22.5 Gy single dose of X-rays in rats.

Tumour necrosis factor-alpha (TNF-α) is known to stimulate the release of prostaglandins and interleukin-1 (IL-1), and PGE_2 inhibits secretion of TNF (Bachwich et al 1986; Kunkel et al 1988). Indometacin enhances radiation-induced TNF production (Petrini et al 1991); thus, prostaglandins produced via the cyclo-oxygenase pathway act as negative regulators of TNF. Suppression of this pathway may have exacerbated the effect of radiation seen by Hofer et al (1992).

Sodium meclofenamate, an anthranilic acid derivative similar to mefenamic acid, is usually given by mouth for the treatment of musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis. This drug not only inhibits prostaglandin synthesis but also interferes with their interaction with cellular receptors. Ambrus et al (1984) treated radiation-induced oesophagitis and cystitis in stumptailed monkeys (*Macaca arctoides*) with varying doses of sodium meclofenamate (5–20 $mg\,kg^{-1}$ daily by gavage), which significantly reduced radiation-induced oesophagitis during the 3 weeks of the study. However, only the largest dose (20 $mg\,kg^{-1}$) had a significant effect in reducing the radiation-induced cystitis. The radiation dose was 20 Gy, delivered as a single dose to the oesophagus or pelvic area.

Administration of flurbiprofen (3.3 $mg\,kg^{-1}\,day^{-1}$) alone or combined with trimetazidine (1 $mg\,kg^{-1}\,day^{-1}$) for 8 weeks, starting 24 h after irradiation, significantly reduced moist desquamation of rabbit skin (Lefaix et al 1992). No beneficial effect was observed with trimetazidine alone.

Enprostil, a synthetic PGE_2, prevented the radiation-induced reduction in the intestinal mucosal surface area and body weight when administered orally (5 $\mu g\,kg^{-1}$) to rats for 2 weeks following abdominal irradiation (Keelan et al 1992). However, the same treatment failed to improve the malabsorption of glucose in the same animals. Northway et al (1988) tested the PGE_1 analogue misoprostol at several doses and via different routes of administration, all starting before start of radiotherapy and continued for about 1 week afterwards, but did not observe any beneficial effect in development of radiation proctitis in rats.

Enzyme inhibitors

On the basis of the effects of angiotensin-converting enzyme (ACE) inhibitors in the prevention and treatment of progressive renal failure, the role of the ACE inhibitor captopril was investigated in the treatment of radiation nephropathy in rats (Robbins & Hopewell 1986) and it was shown that early haemodynamic changes after renal irradiation could be ameliorated. This was followed by a number of studies in lung by Ward and colleagues (1988, 1989, 1992a), who reported that ACE inhibitors could reduce the development of radiation-induced endothelial dysfunction and lung fibrosis. This work was extended to the study of radiation-induced nephropathy (Cohen et al 1992) and it was concluded that early intervention with ACE inhibitors preserved kidney function, reduced proteinuria and increased the survival of irradiated animals. Moulder et al (1993) reported that both captopril and enalapril had comaparable effects in limiting the development of radiation nephropathy in rats. They also showed that blocking angiotension II (ATII) receptors with losartan was more effective than blocking the synthesis of ATII with ACE inhibitors in the prophylaxis of nephropathy (Moulder et al 1996, 1998). Further studies have shown that captopril inhibits histamine- and serotonin-induced vascular permeability in rat skin (Fantone et al 1982) and ameliorates radiation damage to the heart (Yarom 1993).

Kim et al (2004) assessed the effects of ramipril on irradiated optic nerves in rats 6 months after irradiation, and found that at 1.5 $mg\,kg^{-1}\,day^{-1}$ started 2 weeks after irradiation, ramipril significantly modified radiation injury. Rats receiving radiation alone showed a significant lengthening in the mean peak latency in the visual evoked potential, whereas 75% of rats receiving radiation followed by ramipril had evoked potentials that resembled those of normal untreated control rats. The histology of irradiated and ramipril-treated optic nerves appeared nearly normal, while there was significant demyelination in optic nerves of irradiated rats.

Antioxidants

The process of oxidative stress is closely related to a complex cascade of events involving imbalances in the production of certain cytokines. A recent hypothesis for the development of lesions in normal tissue is the existence of sustained oxidative stress or dysregulation of cytokines in irradiated tissues (Tofilon & Fike 2000). Because our antioxidant defences are not completely efficient, and even at their best can only cope with a moderate increase in free-radical formation in the body, it is highly likely that exogenous antioxidants might be beneficial in the case of radiation exposure. Therefore, modulation of oxidative stress caused by irradiation may have a role in amelioration of radiation damage.

Superoxide dismutase The superoxide molecule is an oxygen radical made by adding one electron to the oxygen molecule. The body produces superoxide as a byproduct of metabolism or as part of its defence mechanisms. For instance, activated phagocytes (neutrophils, monocytes, macrophages and eosinophils) produce large amounts of superoxide as a means to kill foreign organisms (Babior & Woodman 1990). Superoxide is involved in ischaemia–reperfusion injury, inflammation and radiation damage. About 1–3% of the oxygen we breathe is converted to superoxide. A normal human being may produce over 2 kg of superoxide molecules per year, and people with chronic infections may produce even larger amounts (Halliwell 1994). Living organisms exposed to ionising radiation produce large amounts of superoxide molecules. Superoxide can also stimulate the production of an IL-1-like substance from human neutrophils (Kasama et al 1989). Neutrophil infiltration is characteristic of many radiation-induced lesions.

Superoxide dismutases (SOD) scavenge and detoxify superoxide by catalysing dismutation and converting superoxide to hydrogen peroxide. These enzymes are found in mitochondria and cytosol. Glutathione peroxidases are major enzymes that remove hydrogen peroxide generated by SOD in cytosol and mitochondria (Chance et al 1979).

The precise mechanisms by which liposomal or free SOD interacts with fibrotic tissue are unknown. While the scavenging effect of SOD can explain its radioprotective effect (when it is made available at the time of irradiation), its actual mechanism of action in reversing chronic conditions such as late skin fibrosis is not clear. Lefaix et al (1996) postulated three possible mechanisms for the effects of SOD. Exogenous SOD may enhance weakened antioxidant capability of irradiated tissue; the attachment of SOD to cellular membrane may initiate an anti-inflammatory process; alternatively, it may inhibit leucocyte and macrophage migration into the extravascular parenchymal tissue that might be expected to initiate fibroblast recruitment and proliferation. These explanations remain to be proven.

In a standardised experimental pig model (Lefaix et al 1996), radiation-induced lesions were produced on the skin, subcutaneous tissue and skeletal muscle with 160 Gy of photon irradiation. This is a large dose that mimics overexposure of humans in radiation accidents involving non-uniform irradiation of skin and subcutaneous tissue. Six months after irradiation, when a fibrotic scar was formed, i.m. injection of 1 mg kg^{-1} of liposomal copper/zinc (Cu/Zn) SOD or manganese (Mn) SOD twice a week for 3 weeks reduced the volume of the scar by 70%. The effect of the treatment was obvious from the first week of treatment. SOD has also been shown to reduce the severity of radiation-induced pulmonary lesions in rats (Malaker & Das 1988). It appears that a difference of 6 h in the biological half-time of liposomal Cu/Zn-SOD (24 h) and free Mn-SOD (18 h) in pigs had no significant effect on the efficacy of SOD treatment, as Lefaix et al (1996) obtained similar results with Cu/Zn-SOD or Mn-SOD. However, Mn-SOD has been reported to be more effective than Cu/Zn-SOD in models of acute inflammation and chronic diseases (Goreckie et al 1991; Parizada et al 1991).

Curcumin Curcumin is a phenolic antioxidant and anti-inflammatory found in the rhizomes of the plant *Curcuma longa* Linn. (Zingiberaceae). This yellow phytochemical has strong antioxidant and free-radical-scavenging activity (Rao et al 1982; Kunchandy & Rao 1990) and it inhibits lipid peroxidation (Joe & Lokesh 1994; Sreejayan & Rao 1994; Sreejayan et al 1997), including radiation-induced lipid peroxidation (Sreejayan et al 1997). Its anti-inflammatory action may be due to its inhibitory effect on arachidonic acid metabolism via lipoxygenase and cyclooxygenase pathways (Stoner & Mukhtar 1995). Furthermore, reports indicate that curcumin inhibits the expression of c-fos, c-jun and c-myc proto-oncogenes (Rao et al 1993; Huang et al 1994; Lu et al 1994; Subramanian et al 1994; Chen & Tan 1998). The biological and pharmacological properties of curcumin have been reviewed (Govindarajan 1980; Tonnesen 1988; Ammon & Wahi 1990; Huang et al 1992). Although reports on the uptake and distribution of curcumin are conflicting, it appears that more than 50% of an oral dose is absorbed, and small amounts appear in the urine (Wahlstrom & Blennow 1980; Ravindranath & Chandrasekhara 1980, 1982). A phase I clinical trial of curcumin has shown that it is non-toxic at oral doses of up to 8 g day^{-1} (Cheng et al 2001) and a daily oral dose of 3.6 g day^{-1} was suggested for phase II evaluation in the treatment of cancer (Sharma et al 2004).

A mixture of curcumin, α-tocopherol and sunflower oil (SFO) was tested in the treatment of radiation-induced oral mucositis in the rat (Rezvani & Ross 2004). The tongues of mature rats were irradiated in situ with 13.5–18 Gy single doses of 2.27 MeV beta-rays from a 5 mm diameter 90 Sr/90 Y plaque. Following irradiation, some of the animals received the test compound (200 mg kg^{-1} curcumin, 20 mg kg^{-1} α-tocopherol in 0.5 mL SFO) by daily gavage until the end of experiments. Daily oral administration of the test compound starting 1 day after irradiation significantly reduced the incidence of radiation-induced mucositis, and a significant dose modification factor (DMF) of 1.24 ± 0.06 was obtained. This was followed by fractionated studies, which gave a DMF of 1.44 ± 0.08 in the same model (Rezvani et al; unpublished data).

α-Tocopherol α-Tocopherol (vitamin E) occurs in membranes and lipoproteins; it blocks the chain reaction of lipid peroxidation by scavenging intermediate peroxyl radicals and converting them to tocopherol radicals. This radical has much less affinity for adjacent fatty-acid side-chains and can be converted back to α-tocopherol by ascorbic acid (vitamin C).

In the treatment of radiation lesions tocopherol has been mostly used in combination with other compounds.

Tocopherol, troxerutine and vincamine administered 24 h after irradiation of the skin of rabbits, for 8 weeks, showed no beneficial effect (Lefaix et al 1992); however, α-tocopherol in combination with pentoxifylline (PTX) was significantly effective in softening and shrinking the fibrotic scar that developed 26 weeks after 160 Gy single dose gamma rays in pig skin (Delanian 1998; Lefaix et al 1999).

Ascorbic acid Ascorbic acid (vitamin C) is a ketolactone and a powerful reducing agent that accelerates hydroxylation reactions in a number of pathways. Ascorbic acid is a cofactor for prolyl and lysyl hydroxylates in the biosynthesis of collagen and is required for optimal function of many enzymes, including proline hydroxylase and lysine hydroxylase (Mussini et al 1967; Puistola et al 1980). However, if ascorbic acid is replaced by other reductants, these enzymes will still exhibit partial, but not maximal, activity (Levine 1986). Ascorbic acid enhances the synthesis of carnitine from lysine; carnitine is essential for the transport of long-chain fatty acids from the cytosol to the site of beta-oxidation in mitochondria (Levine 1986). Absence of ascorbic acid in the diet causes scurvy (Hodges, 1980), capillary fragility due to a defect in the proline hydroxylation step in collagen biosynthesis (Mussini et al 1967), fatigue, hperkeratosis of hair follicles and anaemia (Hodges et al 1971). Ascorbic acid has been associated with certain aspects of the immune system and cholesterol metabolism, but these are controversial (Levine 1986). Ascorbic acid has been considered useful in treating patients with several types of cancer (Cameron & Pauling 1976).

Narra et al (1993) reported that an ascorbic-acid-enriched diet (1% by weight) provided protection of the spermatogonial cells in mouse testes against chronic irradiation (DMF 2.4 ± 0.4). Similar results were obtained by directly injecting a very small dose of ascorbic acid (1.5 μg in 3 μL) into the testes (Narra et al 1993, 1994). Abramsson-Zetterberg (1996) found that adding 5% ascorbic acid to drinking water of mice for 1 week before and 5 weeks after irradiation with low-dose-rate gamma rays did not modify the response, assessed by measuring the frequency of micronucleated normochromatic erythrocytes in peripheral blood. The authors concluded that increasing the intake of ascorbic acid would not be effective in protecting against low doses of ionising radiation to which humans are normally exposed. The dose rate studied by these authors was 44 mGy per day, which is far greater than the dose to which the normal population are usually exposed. Furthermore, there is no evidence to correlate the levels of micronucleated normochromatic erythrocytes and the development of long-term effects of radiation.

Haemorrheological agents

Anticoagulants Use of the anticoagulant heparin as a modifier of radiation damage was one of the earliest attempts in the treatment of radiation-induced normal-tissue lesions. Boys & Harris (1943) considered radiation pneumonitis as an inflammatory process and assumed that prevention of fibrin formation and elimination of thromboses and fibrosis of microvasculature would prevent radiation pneumonitis and subsequent fibrosis. Although these authors claimed an improvement of radiation damage to lung by the application of heparin, Fleming et al (1962) failed to modify the development of radiation pneumonitis in dog lung by the same approach. Moss et al (1960) also reported that heparin failed as a modifier of radiation damage after thoracic irradiation. Another anticoagulant, dicoumarol, was also unsuccessful in modifying the development of radiation pneumonitis in human lung (Macht & Perlberg 1950).

Pentoxifylline The modifying effects of PTX on the effects of radiation on cutaneous tissue have been studied in a mouse foot model (Dion et al 1989). PTX had no effect on acute radiation injury to mouse foot – the severity, and time course of development and recovery, for the acute reactions were identical for PTX-treated and control animals. However, a significant effect on the development of late radiation damage was observed in the PTX group. There were 4/41 (8%) radiation-induced late injuries in animals treated with a daily injection of PTX and 20/48 (42%) in control animals (which received a daily saline injection). In these experiments PTX was administered during the course of irradiation. Lefaix et al (1999) reported significant softening and shrinking of radiation-induced fibrotic scars that developed 26 weeks after 160 Gy single-dose gamma rays in pigs treated with PTX ($13.3\,\mathrm{mg\,kg^{-1}\,day^{-1}}$) and α-tocopherol ($17\,\mathrm{IU\,kg^{-1}\,day^{-1}}$) for 13 weeks. Ward et al (1992b) reported failure of PTX in modifying radiation pneumonitis in rat. The response was monitored by modification of radiation-induced suppression of ACE and plasminogen activator activity and radiation-induced elevation of prostacyclin and thromboxane production. The amount of hydroxyproline in the lung was measured as an indication of pulmonary fibrosis. The severity of epilation and desquamation of skin in the irradiated field was scored weekly as a measure of early skin damage and it was concluded that PTX did not modify the acute skin lesions either.

Clinical studies

Steroids

Abdelaal et al (1989) treated five patients receiving radiotherapy for malignant parotid tumours with 2 mg betamethasone sodium phosphate dissolved in 15 mL water. The solution was used as a mouthwash for 2 min four times a day, starting the day before and continuing throughout 6 weeks of radiation treatment. This treatment prevented mucositis, erythema of the mucosa and radiation-induced discomfort in all five patients. By contrast, neither betamethasone (Baum et al 1989; Triantafillidis et al 1990) nor 5-aminosalicylic acid, the active moiety of sulfasalazine, offered significant benefit in the treatment of radiation proctitis (Triantafillidis et al 1990). Topical application of prednisolone (0.5%) and neomycin (0.5%) twice daily after radiotherapy reduced the area of moist desquamation of skin in patients treated with a single dose of 22.5 Gy X-rays for basal cell carcinoma of the facial skin (Halnan 1962).

NSAIDs

Nicolopoulos et al (1985) reported milder endoscopic oesophagitis and symptomology in patients with lung cancer

who received indometacin after thoracic irradiation. However, histological findings of oesophagitis was no different between indometacin-treated and control groups. The villus: crypt ratio was not affected by indometacin.

Mennie & Dalley (1973) treated 15 women with radiation-induced diarrhoea with 900 mg soluble aspirin four times daily. Diarrhoea that had failed to respond to conventional treatment was either abolished or improved in 12 of these patients. The work was followed by a randomised trial (Mennie et al 1975), who reported that acetylsalicylate effectively controlled the diarrhoea and associated colicky pain and flatulence in 28 women who were receiving pelvic radiotherapy for uterine cancer. Ludgate (1985) treated eight patients with complications following pelvic irradiation with enteric-coated acetylsalicylic acid (Entrophen). While radiation enteritis was improved in all the patients who remained on Entrophen, healing of epithelial ulceration was observed in four out of six cases and improved in one. Patients had to remain on Entrophen: one patient who stopped Entrophen treatment after 6 weeks experienced recurrent diarrhoea and cramps that resolved after restarting the treatment. The mode of action was suggested to be by interference with excessive production of prostaglandin after intestinal irradiation (Mennie et al 1975). Tanner et al (1981) treated radiotherapy- and chemotherapy-induced mucositis in patients with head and neck cancer with aspirin but observed no beneficial effects.

Benzydamine hydrochloride solution ($1.5\,mg\,mL^{-1}$) given to 37 patients as mouthwash and gargle significantly reduced pain and delayed acute oral and oropharyngeal mucositis compared with 30 patients who received only placebo mouthwash (Kim et al 1986). In another study, Epstein et al (1989) reported a beneficial effect of benzydamine hydrochloride in terms of the size and severity of mucositis, but it failed to prove benefit in reducing pain. Samaranayake et al (1988) compared the effectiveness of benzydamine hydrochloride solution and chlorohexidine as mouthwash on a small number of patients and found no difference in terms of mucositis, pain or the presence of microorganisms. However, patient acceptance of chlorohexidine was found to be better. As there was no placebo group, the study does not clarify whether any of the solutions had a beneficial effect.

Enzyme inhibitors Wang et al (2000) reported a retrospective study of incidental use of ACE inhibitors in 26 of 213 patients with lung cancer patients who received ACE inhibitors for hypertension during radiotherapy for lung cancer. These authors concluded that, within the dose range prescribed for hypertension, ACE inhibitors had no beneficial effect on the incidence, and did not delay the onset, of symptomatic radiation pneumonitis among patients with lung cancer receiving radiotherapy. A randomised controlled trial testing whether the ACE inhibitor captopril was effective in mitigating chronic renal failure after haematopoietic stem cell transplantation (HSCT) closed with fewer than the number of patients needed (Cohen et al 2008). The baseline serum creatinine and calculated glomerular filtration rate (GFR) did not differ between the captopril and placebo groups. The 1-year serum creatinine level was lower and the GFR higher in the captopril group compared with the placebo group ($P=0.07$ for GFR). Patient survival was higher in the captopril group than in the placebo group, but this was not statistically significant ($P=0.09$). In subjects who received the study drug for more than 2 months, the 1-year calculated GFR was $92\,mL\,min^{-1}$ in the captopril group and $80\,mL\,min^{-1}$ in the placebo group ($P=0.1$). There was no adverse effect on haematologic outcome. It was concluded that there was a trend in favour of captopril in mitigation of chronic renal failure after radiation-based HSCT.

Antioxidants

Baillet et al (1986) treated 50 patients with established radiation fibrosis with twice-weekly i.m. injection of 5 mg liposomal SOD for 3 weeks and observed a significant softening of the fibrotic tissue in 82% of cases. This was followed by further reports from the same group demonstrating the effects of systemic administration of SOD in the treatment of radiation fibrosis in a heterogeneous population of patients undergoing radiotherapy (Delanian et al 1994).

There are no data on clinical results of the application of curcumin for the treatment of radiation lesions, but there is a growing body of evidence indicating the potential of this naturally occurring substance, as described above.

α-Tocopherol has been mainly used in combination with other drugs (see below).

Haemorrheological agents

Glantz et al (1994) treated 11 patients with late radiation-induced nervous system injuries, all unresponsive to dexamethasone, with full anticoagulation (heparin and warfarin), and reported some recovery of function in five of the eight patients with cerebral radionecrosis and in all the patients with myelopathy or plexopathy. These authors concluded that anticoagulation may arrest and reverse small-vessel endothelial injury and produces clinical improvement in some patients.

Dion et al (1990) treated 15 sites of grade 4 radiation necrosis (four in the oral cavity, four in the mucosa of female genitalia, seven in skin, ranging from 2×3 mm to 3.5×18 cm) with PTX, 400 mg three times a day for 3 months (four times daily in one patient). Necrosis healed completely in 87% (13/15) of cases, one healed partially and one failed to heal. Futran et al (1997) treated 26 patients with radiation-induced normal-tissue lesions after radiotherapy for head and neck malignancies with PTX (400 mg three times a day for at least 3months) and concluded that PTX accelerated the healing of soft-tissue necrosis and reversed late radiation injury. PTX treatment was effective for a significant number of patients: 9/15 (60%) with soft tissue necrosis had complete healing, 3/15 (20%) had partial healing, but there was no effect in 20%. Mucosal pain resolved in all five patients, and fibrosis resolved in 4 out of 6 of those with fibrosis. The latency for the appearance of the lesions was more than 2 months after radiotherapy, and the duration of the lesions ranged from 8 to 41 weeks before PTX treatment.

PTX has been reported to relieve the pain due to radiation fibrosis (Werner-Wasik & Madoc-Jones 1993). This was in a 56-year-old woman treated for T1 adenocarcinoma with excision and re-excision of the lesion, followed by radiotherapy

and reconstructive surgery for severe tissue deficit 7 months after radiotherapy. Pain developed 3 months later. Treatment with PTX (400 mg three times daily for 6 weeks) resulted in complete relief of pain and tenderness of fibrosis. Significant relief of signs and symptoms of radiation mastitis in a small number of patients has also been reported (Steeves & Robins 1998): oedema, erythema and pain started to resolve 3–4 weeks after starting treatment with PTX.

Stelzer et al (1994) reported an overall non-significant trend between the development of radiation lesions and the coffee-drinking habit of 82 women with cervical cancer treated with primary/adjuvant radiotherapy. Higher coffee consumption at the time of radiotherapy was associated with reduced late effects. The incidence of severe late effects was significantly ($P = 0.02$) lower in heavy coffee drinkers. This was attributed to the protective effect of the methylxanthines in coffee.

While there have been reports of negative results with PTX alone (Bianco et al 1991; Kwon et al 2000), beneficial effects of PTX used in combination with α-tocopherol in the treatment of radiation lesions have been reported by Gottlöber et al (1996). This was followed by a report of regression of established radiation fibrosis that had developed 10 years after irradiation, using the same treatment (Delanian 1998).

The efficacy of PTX in combination with α-tocopherol for the treatment of radiation-induced fibrosis was assessed in a double-blind, placebo-controlled, clinical trial involving 24 patients previously irradiated for breast cancer (Delanian et al 2003). Those receiving 800 mg per day PTX and 1000 units per day α-tocopherol for 6 months showed significantly reduced superficial radiation-induced fibrosis. This was followed by another trial by the same authors (Delanian et al 2005), which showed that long-term treatment with a combination of PTX and α-tocopherol significantly reduced radiation-induced fibrosis in patients previously irradiated for breast cancer. These authors recommended a treatment period of longer than 3 years for patients with severe radiation-induced fibrosis.

Discussion

Classic radiobiology, based on target theory for single cells, assumes that radiation kills cells at random, and that the dose of radiation and the radiosensitivity of irradiated cells determine the probability of cell kill. This concept was extended to tissues by viewing normal tissue radiation injury as a result of the sterilisation of clonogenic cells within tissues. According to this concept, tissue-specific function is restricted to functional non-proliferative cells derived from clonogenic cells. Failure of clonogenic stem cells to replace the functional cells, which continue to be lost at a normal rate, results in a gradual depletion of functional cells. When the number of functional cells reaches a critical level, the tissue cannot sustain its function and radiation-induced injury is seen. This concept views the latent period as a reflection of the turnover time of the target cells and considers radiation damage to be both inevitable and untreatable.

Recent evidence obtained using new molecular techniques indicates that a perpetual cascade of molecular changes and cytokine production is initiated immediately after irradiation and persists until expression of radiation injury. A number of processes such as gene expression, dysregulated cytokine production and oxidative stress have already been identified. According to this view of the development of radiation injury, the concept of a latent period is not tenable, and intervention at any stage of the complex process of the development of radiation lesion can potentially modify its progression. At present there is no panacea for radiation injury, but evidence indicates the possibility of modifying radiation-induced normal-tissue damage.

The curability of localised tumours by radiotherapy is compromised by the dose and volume limitations imposed by normal-tissue tolerance, except for radiosensitive tumours. Clearly, increasing normal-tissue tolerance to ionising radiation or improved healing of radiation-induced lesions by modifiers of radiation damage would have significant clinical implications. This includes a variety of pharmacological approaches using both synthetic and naturally occurring substances. There is increasing evidence to suggest the involvement of prostaglandins in the development of radiation injury, and substances that interfere with prostaglandin synthesis and eicosanoid metabolism appear to be the most widely studied modifiers of radiation damage. These include steroids, essential fatty acids and NSAIDs. However, several problems prevent the translation of existing evidence into clinical practice. These include the limitations of animal models that do not directly translate into humans, the conflicting results reported with some modifiers of radiation damage, and the toxcitiy of these substances and the irradiation doses used in published reports. Conflicting results may arise partly because of differences in the pathophysiologic processes involved in the development of radiation lesions in different tissues, and in the markers used to assess the efficacy of treatment agents. These differences indicate the complexity of the development of radiation damage and perhaps the multiplicity of mechanisms involved.

There appears to be a tissue-specific response for different NSAIDs. While some NSAIDs such as indometacin and aspirin prove to be beneficial after sublethal TBI and local skin irradiations or mucosal reactions in radiation enteritis, they show adverse reactions after lethal doses and irradiation of some other organs such as the rectum and oral mucosa. Although beneficial effects of using NSAIDs have been reported, a major draw back of using NSAIDs such as aspirin in the treatment of radiation enteritis is that the patients have to remain on the medication. Care must be taken in the administration of these substances for the management of different aspects of radiation damage.

Dose modification factor

The effectiveness of radiation modifiers is usually expressed in terms of the DMF – the ratio of the radiation dose in the presence of modifier and the radiation dose in the absence of modifier, required to produce the same level of injury. A DMF value above 1 is indicative of a beneficial effect, a value of 1 indicates no effect; values below 1 indicate detrimental effect. By definition, DMF is the same as the dose reduction factor used in the literature. It is customary for DMFs to be calculated from comparison of the dose of

radiation that is effective in 50% of subjects exposed to radiation (ED50) and the dose that proved lethal in 50% of animals in quantitative analyses, or from comparison of the response for a known dose at a certain time point. In order to produce a meaningfully measurable level of damage, relatively larger radiation doses are used in radiobiological research; these doses are often substantially larger than the doses used clinically in radiotherapy for cancer. The results of such studies might be applicable to the case of accidents but not directly to radiotherapy. The effects of modifiers of radiation damage should be demonstrated for doses comparable to clinical doses before the application of these agents in clinical practice. However, lower incidence of endpoints at the lower-dose region of the dose–effect curve, where uncertainties are much greater, is a practical difficulty. This difficulty can be overcome by studying the effects of modifiers of radiation damage at different dose points to demonstrate their efficacy at various dose levels. A true modifier of radiation damage should shift the dose–response curve towards higher doses by a constant fraction. Otherwise, DMF will be a radiation-dose-dependent parameter. Furthermore, the majority of the published experimental results on the efficacy of substances used for the treatment of radiation damage involve large single irradiation doses. Therefore, although encouraging, the compiled evidence has only limited value, except perhaps in the treatment of patients who have had a radiation accident or those with complications as a result of radiotherapy for cancer. Studies involving full dose–effect curves are required to distinguish true modifiers of radiation damage, with a significant DMF that is constant for all dose levels. DMFs in excess of 1.13, and sometimes as high as 1.51, have been observed. This might appear modest, but, in reality, dose increases of 10–20% above the present radiotherapy dose would, for many tumours, provide significant local tumour control by radiotherapy. This reflects the steep dose–response relationship for both normal tissues and some tumours. Furthermore, as fractionated radiotherapy is widely used in curative radiotherapy, the efficacy of modifiers of radiation damage needs to be assessed in relation to fractionated schedules. Single-dose data cannot be translated to clinical use, particularly for dose-escalation in radiotherapy, unless further results involving multiple small fractions, comparable to radiotherapy regimens used for the treatment of cancer, are made available.

Choice of model

The choice of model used to study the effects of modifiers is very important. For example, the results for the efficacy of ascorbic acid in modification of radiation damage are conflicting, and the overall evidence is not conclusive. Most of these studies have used the mouse as an experimental model, but this may not be a suitable model to study the effects of ascorbic acid. Although humans are unable to synthesise ascorbic acid, most other mammals, including mice, can do so from glucuronic acid or galactonic acid derived from glucose (Chatterjee 1970). Mice are one of the most efficient mammals in producing its own ascorbate – they can synthesise ascorbic acid at a rate of 33.6–226.0 $mg\,kg^{-1}$ body weight per day. Other animals unable to synthesise ascorbic acid include non-human primates, the guinea pig, Indian fruit bats and several varieties of bulbuls. The inability of humans to synthesise ascorbic acid may reflect lack of the enzyme glunolactone oxidase or an equivalent enzyme (Levine 1986).

Conclusion

Steroids

Evidence on the use of steroids in the treatment of radiation injury is contradictory. Some authors have even reported adverse reactions of using corticosteroids for the treatment of radiation damage (Berdjis 1960; Cladwell 1971). The majority of the older publications reporting the results of steroid therapy suffer from poor study design and lack of randomised procedures. However, evidence based on recent reports and randomised studies does not support beneficial effects of steroid therapy. It appears that, at best, steroids may delay the development of acute lesions and perhaps reduce the severity of lesions (Marshall 1953), but without reducing the incidence of radiation lesions, particularly late effects (Moss et al 1960). A large number of reports on the administration of steroids before or during radiotherapy are available. This will reveal the drug's radioprotective properties rather than its modifying capabilities. Since the aim of this article was to review the efficacy of post-irradiation treatments, these reports are not included here. Michalowski (1992) has reviewed this area.

NSAIDs

Results relating to the efficacy of NSAIDs in the treatment of radiation-induced lesions to normal tissue are conflicting. It should be borne in mind that not all NSAIDs have the same mode of action, and they may have different actions on the response of different tissues to radiation. Thus, some conflict could arise from using unsuitable drugs. While inhibition of prostanoid production via inhibition of cyclo-oygenase after irradiation appears to be beneficial in some tissues, it is undesirable in others. Overall, NSAIDs, notably aspirin and perhaps indometacin, appear to be effective in the treatment of acute radiation damage in some tissues. NSAIDs have been shown to have beneficial effects, such as indometacin after sublethal TBI and local skin irradiations, and aspirin in the treatment of mucosal reaction in radiation entretitis. However, others have adverse reactions after lethal radiation doses and irradiation of some other organs such as the rectum. This inconsistency in the response of irradiated tissues to NSAIDs is a cause for concern. Care must be taken in the administration of these substances for the management of different aspects of radiation damage. NSAIDs can be categorised into three groups as described by Twomey & Dale (1992): those that increase superoxide production (diclofenac, meclofenamate, mefenamic acid), those that have no effect (ketoprofen) and those that decrease superoxide production (aspirin, phenylbutazone, piroxicam). The mode of action of the NSAIDs that enhance the superoxide response is unlikely to relate to inhibition of the cyclo-oxygenase pathway. Perhaps this group of NSAIDs will not be suitable for the treatment of radiation lesions and this might be an explanation for the adverse reaction of diclofenac treatment after TBI in mice (Hofer et al 1992). On the other hand NSAIDs such as indometacin, salicylic acid and aspirin (acetylsalicylic acid) might be more suitable for this purpose as they have been

shown to inhibit superoxide generation by human neutrophils (Umeki 1990).

Enzyme inhibitors

Despite clear understanding of the physiology of the renin–angiotensin system, the mechanisms of action of ACE inhibitors in reducing radiation-induced nephropathy are not fully understood. While there is ample experimental evidence to support the efficacy of ACE inhibitors (captopril and enalapril) and the ATII receptor antagonist losartan in amelioration of radiation-induced nephropathy, their clinical efficacy needs to be proven. A recent clinical trial (Cohen et al 2008) did not show statistically significant benefit and suggested only a trend in favour of captopril in mitigation of chronic renal failure after radiation-based HSCT.

Antioxidants

Treatment results with SOD are remarkable. Most striking is the subsequent stability after patients have stopped treatment (Delanian et al 1994). Evidence on the efficacy of ascorbic acid is not convincing, but the data for the efficacy of α-tocopherol in combination with PTX in the treatment of late radiation damage are promising.

Although some studies show positive evidence for the efficacy of ascorbic acid in modifying radiation damage, overall the evidence is not conclusive. However, considering that some positive results have been obtained, even using unsuitable models, it is possible that some patients may benefit from large doses of ascorbic acid as part of a treatment plan.

It appears that α-tocopherol is mainly effective in combination with other drugs in the treatment of radiation lesions.

There are no clinical data relating to the application of curcumin for the treatment of radiation lesions, but a growing body of evidence indicates the potential of this naturally occurring substance. Considering the antitumour characteristics of curcumin, this substance may be an ideal modifier of radiation damage.

Haemorrheological agents

While there have been reports of negative results with PTX alone, evidence for a beneficial effect of PTX used in combination with α-tocopherol, both experimentally and clinically, are mounting, particularly in relation to treatment of the late effects of radiotherapy.

General conclusion

It must be borne in mind that this is not an evidence-based systematic review; thus it is not possible to give recommendations on the treatment of specific lesions. Furthermore, different tissues respond differently to radiation, and a number of different pathological processes occur after radiotherapy. These include early molecular changes and cytokine production, which result in the development of an acute inflammatory reaction, followed by the development of progressive ischaemia and loss of stem cells, ultimately resulting in the long-term effects of irradiation and fibrosis. However, the limited evidence available suggests that radiation insult, like many other tissue injuries, is amenable to pharmacological intervention. Although, late effects such as skin or pulmonary fibrosis have always been considered to be irreversible, the evidence suggests that even these lesions can be treated. Therefore, radiation lesions ought to be considered as other pathological conditions, and radiation medicine should utilise the findings of the other branches of medicine by exploiting common pathophysiologial developments between radiation lesions and other ailments. Systematic screening of synthetic and natural substances may lead to the identification of other substances that can modify the response of normal tissues more effectively. Alternatively, pharmaceutical agents can be designed specifically to interfere with the many pathways involved in the development of radiation injury.

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