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REVIEW ARTICLE

Radiation-induced lung injury: latest molecular developments, therapeutic approaches, and clinical guidance

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Abstract

Cancer research has advanced throughout the years with respect to the personalization of the treatments and to targeting cancer-related molecular signatures on different organs. Still, the adverse events of the treatments such as radiotherapy are of high concern as they may increase the mortality rate due to their severity. With the improved efficiency of cancer treatments, patient survival has been increasing. Consequently, the number of patients with adverse effects from radiotherapy is also expected to increase in the forthcoming years. Therefore, approaches for personalized treatments include the elimination of adverse events and decreasing the toxicity in healthy tissues while increasing the efficiency of cancer cytotoxicity. In this context, this paper aims to discuss the recent advances in the field of thorax irradiation therapy and its related toxicities leading to radiation pneumonitis in cancer patients. Molecular mechanisms involved in the radiation-induced lung injury and approaches used to overcome this lung injury are discussed. The discourse covers approaches such as therapeutic administration of natural products, current and prospective radioprotective drugs, and applications of mesenchymal stem cells for radiation-induced lung injury.

Keywords Cancer · Lung · Radiation pneumonitis · Fibrosis · Radiation · Therapy

Introduction

Radiation therapy is crucial in eradicating tumors. However, damage signals in irradiated tissues and in tissues experiencing out-of-field effects can cause serious side effects and are often a restrictive aspect in radiation therapy. These damage signals, including increased inflammatory responses, can increase the risk of other primary tumors due to constant free radical production, activation of oncogenes, and repression of the tumor suppressor genes [1, 2]. Indeed, it was established that ionizing radiation (IR)-dependent generation of free radicals impacts mitochondrial functions by upregulating cyclooxygenases, lipoxygenases, nicotinamide adenine dinucleotide phosphate oxidase, and nitric oxide synthase [1, 3]. Toll-like receptors and cytokines, such as IL-1β, TNF-α, TGF-β, IL-4, and IL-13, are considered as targets for drug-based radioprotection of healthy tissue [1, 3].

As the lung is a radiation dose-limiting organ, radiation dose and patient-related dosimetric factors must be considered and associated with the radiographic and clinical toxicity in order to circumvent possible damages to the healthy lung tissue [2, 4]. Radiation-induced lung injury not only impairs the health of the cancer patients and lifestyle but also reduces the effects of radiotherapy [5]. In detail, thorax irradiation induces radiation pneumonitis during the early phase and fibrosis in the later phase [6, 7]. In addition to lung toxicity, radiation therapy for lung cancer can also result in radiation-induced cardiac injury, which can affect the pericardium, muscle, the electrical conduction system, valves and vasculature, and other cardiac structures [8]. The radiation-induced effects on the vasculature are

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considered the most important for pathophysiologic correlations of heart toxicity. Additionally, fibrosis is an important adverse event of radiation therapy, especially in small vessels and endothelial injury, causing arterial diseases mainly in patients that are predisposed with lipid dysregulation and atherosclerosis [8].

Administration of various candidate agents either pre- or post-irradiation of lung attracted the interest of many researchers in respect of protecting, preventing, and/or recovering reactive oxygen stress caused directly by IR-induced lung injury. Herein, we discuss the molecular mechanisms involved in the radiation-induced lung injury and the therapeutic approaches used to overcome this lung injury.

Mechanisms of radiation toxicity in diseased and healthy tissues: cellular and molecular levels

Patient samples and studies in animal models show a complex response of the lung to irradiation with multiple interactions including those of epithelial cells, endothelial cells, fibroblasts, extracellular matrix molecules, and infiltrating immune cells [9]. Despite the ongoing research in identifying the signaling of DNA damage in non-targeted tissues, there is still uncertainty about the underlying mechanisms. This is because signaling pathways are frequently tissue and organ specific. The most studied contributing factors in DNA damage of oxidative stress include reactive oxygen species (ROS), reactive nitrogen species, ROH, NO, and peroxynitrite, in addition to lysosomal enzymes, cytokines, exosomes, and miRNAs [10]. Radiotherapy can disrupt cellular functions and cause genomic instability and radiation carcinogenesis, all of which are contributed by multifactorial phenomena. There is a complexity of interactions between multiple factors following radiation, and these include radiation-induced bystander and non-targeted effects to various cellular, molecular, tissue, and organ targets. Understanding these effects can lead to insights on radiation therapy and its related adverse events [10]. This will also lead to the identification of biomarkers and thereafter the designing of personalized therapeutics targeting the molecular and cellular characteristics of radiation-induced bystander and non-targeted effects [10].

Studies showed that the up- or downregulation of affected genes, enzymes, and proteins and the epigenetic regulation thereof following irradiation are based on exogenous clastogenic factors. These exogenous factors are secreted after the irradiation of tissues and organs into the bloodstream and include free radicals, cytokines, exosomes, miRNAs, protein kinases, and oxidized DNA [10]. Besides inflammation, various other activities related to the redox system are induced, such as increased mitochondrial activity and dysregulation of antioxidant protein activity in bystander-effect-targeted cells, tissues, and organs [10, 11]. Free radicals such as ROS generate DNA breaks and mutations which can result in the epigenetic hypomethylation/upregulation of oncogenes encoding proteins such as c-MYC, Ras, and subunits of exosomes [10]. Importantly, even without DNA damage, exosomes and miRNAs can lead to an increased probability of the development of radiation-induced carcinogenesis.

Activation of the immune system, including the macrophages for phagocytosis, primes the secretion of anti-inflammatory cytokines like IL-10 and TGF-β [12]. Release of necrotic molecules, such as oxidized DNA and high mobility group box 1 (HMGB1), results in the attraction and activation of lymphocytes. These molecules activate the expression of the nuclear factor-κB and the signal transducer and activator of transcription (STAT) or signal transduction proteins such as mitogen-activated protein kinases (MIPK), intercellular adhesion molecule 1 (ICAM1), and the vascular cell adhesion molecule 1 (VCAM1) [12]. Subsequently, inflammation-mediating proteins and pro-oxidant enzymes are up-regulated, including cyclooxygenase-2, iNOS, and NADPH oxidase, which then lead to increased production of ROS and further stimulation of additional free radicals by the mitochondria [12]. This cascade is known as the ROS-induced ROS cascade [12].

Continuous ROS release plays a significant role in development of both early and late IR-induced adverse effects [12]. An in vivo study in mice demonstrated that exposing them to IR increased ROS release in the hematopoietic bone marrow cells for 8 weeks [12]. Specifically, the upregulation of NOX4 and NOX2 was identified to be responsible for the continuous ROS release in mice bone marrow cells, while NOX4 inhibition offered a radioprotective effect [12]. On the other hand, inhibition of both NOX4 and NOX5 was shown to alleviate ROS release and oxidative DNA damage in human fibroblast cells exposed to IR. A radiation-specific mRNA profile occurs as a result of miRNAs, which suppresses DNA methyltransferases and thus impacts the maintenance of hypomethylation and causes upregulation of oncogenes [12]. Upregulation of TGF-β can lead to the cascade activation of additional miRNAs which affects bystander cells, tissues, and organs by amplifying genomic instability [10, 11]. As a consequence, chronic oxidative injury following exposure to IR is an important contributing factor in radiation toxicity. Fibroblast viability was also assessed in another study following lung irradiation in idiopathic pulmonary fibrosis patients and non-idiopathic pulmonary fibrosis patients, and it was identified that idiopathic pulmonary fibrosis fibroblasts were significantly more resistant to apoptotic death when compared with non-pulmonary fibrosis fibroblasts [4].

Macrophage infiltration is associated with lung fibrosis following irradiation: Meziani et al. demonstrated that there

are distinctive pathways of macrophage infiltration when comparing intestinal macrophages versus alveolar macrophages in radiation-induced fibrosis. They also identified the CSF1/CSF1R pathway as a novel therapeutic candidate for radiation-induced fibrosis inhibition. The results were drawn from both a preclinical mouse model (C57BL/6 mice) following 16 Gy thorax irradiation and also from using human lung biopsies from patients undergoing irradiation of the thorax, and it was established that there were high numbers of infiltrating macrophages in both cases [13].

Radiation toxicity in diseased and healthy lung tissues: clinical trials

Besides causing damages to the IR-treated tissues, radiation toxicity also occurs in normal tissues and the respective mechanisms were investigated by many researchers. Exposure to IR results in the generation and release of ROS and contributes to inflammatory responses and to chronic production of free radicals that have been associated with side effects such as fibrosis, pneumonitis, dermatitis, and ulcers [12]. Radiation-induced cell death can result from the release of ROS, as well as by means of a mitotic catastrophe, apoptosis, necrosis, autophagy, and senescence. These effects are in relation to the radiation dose: IR of less than 1 Gy results in a higher apoptosis-to-necrosis ratio, while IR of higher than 2 Gy results in greater necrosis [12]. IR-induced pulmonary toxicity is a frequent fatal side effect (up to 30%) in patients exposed to thorax radiotherapy [14]. Thus, the dose of radiation therapy is a strong limiting factor, especially in lung cancer patients, as pneumonitis was reported at a rate of 3–13% [14]. It is important to recognize high-risk patients and to develop the means to overcome the side effects, i.e., personalized treatments with dose-volume parameters (volume of lung receiving > 20 Gy (V20 Gy)), anatomic lung constraints (mean lung dose (MLD)), and administration of protective therapeutics [14]. Notably, dose-volume parameters of V20 < 20% were still noted to result in an 18.4% risk of clinical-grade pneumonitis [14].

Stereotactic body radiotherapy, also known as stereotactic ablative radiotherapy, is considered the standard treatment option for early stage inoperable non-small-cell lung carcinoma [15]. Predictor candidates for radiation pneumonitis (grade ≥ 2) were chosen with the aim to rank risk patients for radiation pneumonitis, and these include the anatomic and functional lung dosimetric parameters [16]. Substantial differences were noted between anatomic and perfused lung dosimetry parameters, while the study indicated that the pairing of an anatomic and functional dosimetric parameter may improve the prediction accuracy [16]. Another study for prediction of radiation pneumonitis investigated both patients with and without pneumonitis and concluded that there were differences in anatomic and functional lung dosimetry [14]. A study using pretreatment lung function heterogeneity metrics and lung dosimetry identified MLD, V20, pMLD, pV20, pF20, and SF20 as significant univariate predictors of grade ≥ 2 pneumonitis, while MLD, V20, pF20, and sF20 could offer independently predictive information [14]. Upregulation of pro-oxidants, i.e., iNOS, NADPH oxidase 1 and 4, COX-2, and increased superoxide release by the mitochondria were all related to the development of pneumonitis and fibrosis [12].

In studying radiation pneumonitis, stereotactic ablative body radiotherapy was delivered as 45–60 Gy over 3–4 fractions (> 100 Gy in BED) and it was concluded that the incidence of symptomatic radiation pneumonitis was acceptable with most patients having grade II radiation pneumonitis [17]. Predictors to symptomatic radiation pneumonitis were found to be iGTV over 4.21 mL and planning target volume (PTV) of over 14.35 mL [17]. Another study correlated the predictive factors for radiation-induced pneumonitis in patients exposed to stereotactic body radiation therapy. When comparing the results of the patients with or without radiation pneumonitis, there was no obvious difference based on the age. However, there was a significant difference when considering PTV, MLD, total MLD, and V5, V10, V20, and V40 (the percentage of lung volume exceeding 5, 10, 20, and 40 Gy) [18]. The authors concluded PTV, MLD, total MLD, V5, V10, V20, and V40 as the risk factors for the incidence of radiation pneumonitis following stereotactic body radiation therapy in lung tumor. Among these factors, V5 and V20 have the greatest potential for the prediction of radiation pneumonitis incidence [18].

A study was performed with stage II to III non-small-cell lung cancer patients with concurrent development of grade ≥ 3 cardiac events in order to identify the rate of cardiac events. The patients were exposed to the median radiation dose of 70 Gy, with 84% of them receiving concurrent chemotherapy and with 27% having had preexisting cardiac disease [19]. In this study, both disease progression (more common) and grade ≥ 3 cardiac events were related to decreased overall survival while cardiac event rates were associated with preexisting cardiac disease and higher mean heart dose [19]. In another study, stage III non-small-cell lung cancer patients received dose-escalated radiation therapy from 70 to 90 Gy (median, 74 Gy) with the aim to study the cardiac event correlation with radiation therapy [20]. This study established that higher radiation doses in the heart were associated with cardiac events especially after high-dose thoracic radiation therapy with worse overall survival. There was an independent association with heart dose and baseline cardiac risk [20]. It must be noted that the cardiac risks should be considered against tumor eradication, despite the fact that heart disease caused by radiation side effects can be controlled by adjusting radiation dose [19].

Radiation-induced lung damage in lung cancer patients following 12 months after radical chemoirradiation included parenchymal change, pleural changes, and lung shrinkage, while reticulation and traction bronchiectasis were also common. The results were captured in CT scans of 33 patients of a phase I/II clinical trial of isotoxic chemoradiation, among which 6 patients were excluded owing to lung collapse and abscess while the rest of the 27 patients had radiological evidence of lung damage [21]. Furthermore, clinical pulmonary toxicity was evaluated in patients with central lung tumor in an observational study. A pooled analysis along with radiographic bronchial toxicity (RBT) following irradiation therapy was performed for comparing normal tissue toxicity and identifying toxicity predictors by collecting data from 195 patients, among which clinical grade 3 toxicity was apparent in 24 patients and RBT in 55 patients, 12 months post-treatment [2]. Using multivariate analysis, it was found that the target volume overlapping the trachea/main stem bronchus, chronic obstructive pulmonary disease, and the total $V_{130\,Gy,EQD}$ were significant predictors for clinical toxicity. The same group confirmed a dose-related association of clinical and radiographic toxicity following dose-specific irradiation (high) in central lung tumors; however, additional data are required from prospective studies to validate the results [2]. A study with 46 NSCLC patients with high and low levels of Ape-1, ICAM-1, and IL-17A prior to treatment with irradiation (examined with ELISA) indicated that high levels of Ape-1, ICAM-1, and IL-17A are related to an increased risk of radiation pneumonitis. Additional research must be performed to indicate and verify the prognostic value of these molecules [22].

Recent advances in the treatment of radiation-induced lung injury

In terms of radiation-induced lung injury and the subsequent acute radiation syndrome, the therapeutic approaches to overcome such an undesirable result cannot be ethically tested in humans. For this reason, the FDA has suggested guidelines with respect to the design and implementation of animal models to support licensure for candidate medical therapeutics. These guidelines have been elucidated in detail by MacVittie et al. [23]. The only FDA-approved cytoprotective agent for head and neck radiotherapy is amifostine, but mixed effectiveness limits its usage in lungs [24, 25]. Presently, there is no effective FDA-approved routine clinical radioprotective strategy for controlling IR-induced lung injury, including irradiation-induced pulmonary fibrosis [5, 23, 26]. Consequently, there is a great focus on agents that are clinically applicable for use in irradiation-induced lung injury, induced not only due to irradiation-related therapies but also irradiation accidents.

Natural and synthetic radioprotective agents for radiation-induced lung injury

Many antioxidants have been studied for their radioprotective properties (see Table 1). An example is hesperidin (HES) which was assessed in rat models to decrease radiation pneumonitis and radiation fibrosis in lung tissue [27]. Also, the anti-inflammatory melatonin is an immune stimulator and radioprotector which acts by directly or indirectly scavenging free radicals [28]. It was recently demonstrated in rats that pre-irradiation administration of melatonin improved the IR-induced damage by reducing the enzyme activities of glutathione peroxidases, 3,4-methylenedioxyamphetamine (MDA) levels, and superoxide dismutase (SOD) in lung tissues, while TGF-β–microRNA-21 or TGF-β-COX-2 may also be involved in melatonin-mediated radioprotection [29]. In animal experiments, research in monkeys receiving whole-thorax lung irradiation and administration of a metalloporphyrin antioxidant, AEOL 10150, showed promising results as an effective medical countermeasure against radiation-induced lung injury [23]. Polydatin (PD) was suggested as a novel potential radioprotector as it mitigated radiation-induced lung damage caused by inflammation and late fibrosis by inhibition of the epithelial–mesenchymal transition and overexpression of sirtuin 3 [6].

Importantly, Pan and colleagues identified navitoclax (ABT-263) as an agent that can reverse IR-induced pulmonary fibrosis even in the late stages when the disease has progressed considerably. ABT-263 is a B cell lymphoma 2/extra-large (Bcl-2/xl) inhibitor and a newly identified senolytic drug that can be considered for the treatment of pulmonary fibrosis [30]. Another study administered the monoclonal antibody FG-3019 in a mouse model to characterize pulmonary fibrosis with the aim to block the connective tissue growth factor (CTGF). Indeed, FG-3019 prevented (~ 50%–80%) or reversed (~ 50%) lung remodeling and improved the overall health of the mice [31]. The CTGF antibody, pamrevlumab, also had positive effects in pulmonary radiation injury mice models [32]. Similarly, the TGF-β inhibitor SM16 or angiotensin-converting-enzyme inhibitor (ACEi) captopril was efficient in reducing IR-induced lung injury in murine models, clinical randomized controlled trial observations, and larger retrospective series [24]. The same paper discussed one of the earliest applications of SOD in humans with the use of the liposomal SOD, Lipsod, where there was a regression in pulmonary fibrosis in a study of 34 patients and the treatment was reported to be well tolerated [24].

Another study on captopril recruited patients based on stage II-IIIB non-small-cell lung cancer, stage I central non-small-cell lung cancer, or limited-stage small-cell

Table 1 Different natural products and their radioprotective mechanisms

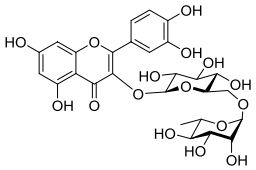
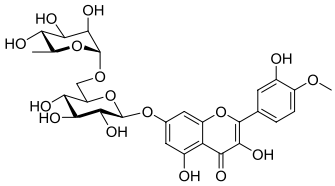
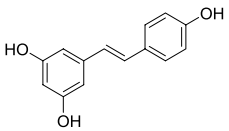
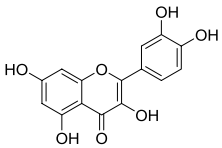
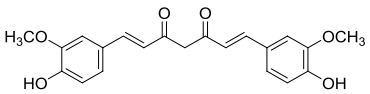
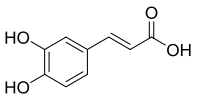
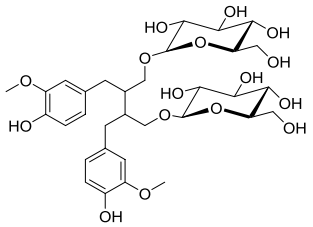
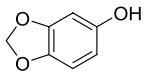
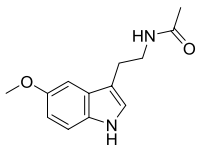
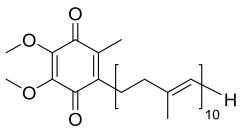
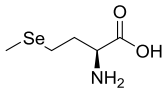
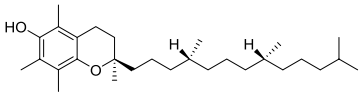
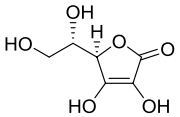
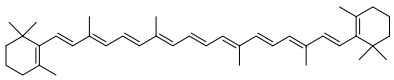
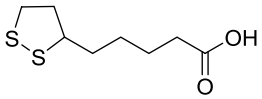
Agent	Structure	Investigated in	Dose	Mechanisms of action
Rutin		Mice	50 mg/kg	ROS scavenging, stimulation of antioxidant enzymes
Hesperidin		Mice, rats	No toxicity up to 100 mg/kg	Prevention of immune cell recruitment, stimulation of antioxidant enzymes
Resveratrol		Mice	No toxicity up to 100 mg/kg	Suppression of NOX4, simulation of Sirt-1, stimulation of antioxidant enzymes
Quercetin		Mice	No toxicity up to 100 mg/kg	Inhibition of NF-κB and MAPKs, stimulation of antioxidant enzymes, scavenging ROS
Ocimum sanctum	–	Mice	200 mg/kg	Scavenging ROS, stimulation of antioxidant enzymes
Curcumin		Humans	Up to 8 g/day	Targeting NF-κB and inflammatory cytokines, scavenging ROS
Caffeic acid		Mice	30 mg/kg	Scavenging ROS, recycling GSH, suppression of inflammatory cytokines
Secoisolariciresinol diglucoside (SDG)		Humans	No toxicity up to 3 g/kg	Inhibition of NLRP3 inflammasome
Sesamol		Mice	No toxicity up to 100 mg/kg	Scavenging ROS, activation of GSH and CAT
Melatonin		Humans	20 mg/kg. No toxicity up to 100 mg/kg	Scavenging ROS and NO, stimulation of antioxidant enzymes, inhibition of inflammatory responses
Coenzyme Q10		Rats, humans	No toxicity up to 100 mg/kg	Stimulation of SOD and CAT
L-Selenomethionine		Humans, rats	1 mg per day	Scavenging ROS, activation of natural antioxidants and antioxidant enzymes

Table 1 (continued)

Agent	Structure	Investigated in	Dose	Mechanisms of action
α-Tocopherol		Mice	100 mg/kg	Scavenging ROS, stimulation of interleukin-6 and G-CSF
Ascorbic acid		Mice	No toxicity up to 3 g/kg	Scavenging ROS
β-Carotene		Humans	40 mg daily	Inhibition of iNOS and COX-2. Downregulation of NF-κB, stimulation of SOD and CAT
α-Lipoic acid		Mice	No toxicity up to 100 mg/kg	Inhibition of NF-κB, scavenging ROS, restoration of GSH, recycling of natural antioxidants

ROS reactive oxygen species; *GSH* glutathione; *SOD* superoxide dismutase; *CAT* catalase; *G-CSF* granulocyte-colony stimulating; *NOX4* NADPH oxidase 4; *COX-2* cyclooxygenase-2; *iNOS* inducible nitric oxide synthase

lung cancer. Those that were eligible for randomization following the commencement of radiotherapy were administered either captopril or standard care for 1 year with captopril escalation to 50 mg three times a day. Out of the 33 patients that were randomized among the recruited 81 patients, only the data of 20 patients were analyzed and it was concluded that the incidence of grade II pulmonary toxicity 23% was due to radiation therapy in the observational arm and 14% in the captopril arm [33]. A retrospective study evaluated clarithromycin in patients with high-risk factors for radiation pneumonitis, increased Krebs von Lungen-6, and/or surfactant protein D for identifying whether clarithromycin alleviated irradiation-induced pneumonitis (a total dose of 40 to 60 Gy in 5 to 10 fractions and followed ≥ 6 months). Multivariate analysis from the results of 580 patients established that clarithromycin mitigated radiation pneumonitis; however, further studies are required to confirm its efficacy [7]. The various clinical trials related to post-radiation toxicity and radioprotective agents are presented in Table 2.

The role of mesenchymal stem cells in the treatment of radiation-induced lung injury

In addition to natural antioxidants and antibodies, mesenchymal stem cells (MSCs) are also known for their immunomodulating and regenerating properties [5]. Thus, MSCs have been considered for treatment of radiation-induced lung damage as they can differentiate to lung alveolar epithelial cells and secrete anti-inflammatory factors. In gene therapy, they can act as cell therapy vehicles [5]. In a mouse model of radiation-induced pneumopathy, the injection treatment with MSCs early after irradiation showed a therapeutic potential by restoring the radiation-induced reduction of the antioxidant enzyme SOD1 levels by an MSC-secreted factor [9]. This administration also counteracted the radiation-induced vascular damage and endothelial cell loss. Furthermore, they protect the lungs from radiation-induced late damage, as demonstrated in preclinical studies [9]. Challenges with respect to MSCs-therapeutic approaches included the concentration (optimal dosage) and time of exposure at the injury site, while the administration route and general safety still require evaluation since the MSCs may have dual effects, i.e., in the protection and in the amelioration of lung injuries [5, 34].

Genetically modified stem cells also received great attention for protection and reduction of lung injury following irradiation in experimental models. In mice, *manganese superoxide dismutase* (*MnSOD*) gene-modified MSCs transplants significantly reduced lung inflammation and protected the lungs from damage caused by cellular apoptosis [26]. The MnSOD enzyme catalyzes the dismutation of O_2^- into oxygen and hydrogen peroxide and protects mitochondria against ROS [26]. In addition to drug or stem cell administration approaches for radiation therapy, other approaches include functional lung imaging, namely radiomics, which is used for analyzing the quantitative features from image data. This approach has already been applied in pulmonary toxicity studies and analysis of 48 diagnostic thoracic tomography scans of fourteen patients with the aim to measure post-irradiation

Table 2 Clinical trials related to post-radiation toxicity and radioprotective agents

Clinical trials/studies	Patients and methods	Results and conclusion	References
Cardiac toxicity after radiation therapy (RT)	127 patients with stage III non-small-cell lung cancer received dose-escalated RT to 70 to 90 Gy (median, 74 Gy) in six trials Cardiac risk was assessed by noting baseline coronary artery disease and calculating the World Health Organisation/International Society of Hypertension score. Competing risks analysis was used	RT-associated cardiac toxicity after treatment of stage III non-small-cell lung cancer was independently associated with both heart dose and baseline cardiac risk, and heart doses should be minimized	[20]
Dose escalation of a curcuminoid formulation: clinically significant impact on radiotoxicity	Randomized and double-blinded trial of oral (2.0 g thrice daily) curcumin tablets ($n=14$) vs placebo ($n=16$) in breast cancer RT	Seven of 24 subjects (30%) experienced only minimal toxicity that did not appear to be dose related. The tolerance of curcumin in high single oral doses was excellent	[37, 38]
Treatment with melatonin for glioblastoma patients undergoing radiotherapy: better survival with minimal side effects	Melatonin treatment (20 mg daily) for 30 glioblastoma patients undergoing radiotherapy resulted in better survival and minimal side effects. Patients received fractionated radiotherapy with a total dose of 60 Gy	RT-related toxicities were lower in patients concomitantly treated with melatonin. RT plus melatonin may prolong the survival time and improve the quality of life of patients affected by glioblastoma	[12, 39]
Melatonin effect on the occurrence of radiation-induced dermatitis in patients with breast cancer that underwent radiotherapy	Phase II, prospective, randomized, placebo-controlled double-blind study Patients who underwent breast-conserving surgery for stage 0–2 breast cancer were randomly allocated to melatonin emulsion (26 women) or placebo (21 women) twice daily during RT and 2 weeks following the end of radiotherapy Women received 50 Gy whole-breast RT with 2 Gy/fx using computed tomography-based 3D planning	The occurrence of acute radiation dermatitis was significantly lower (59% vs. 90%, $P=0.038$) in the melatonin group Patients treated with melatonin experienced significantly reduced radiation dermatitis compared to patients receiving placebo	[12, 40]
Cardiac events, i.e., cardiac injury and radiation therapy, for locally advanced non-small-cell lung cancer (NSCLC)	125 patients met eligibility criteria; median follow-up was 51 months for surviving patients Median prescription dose was 70 Gy, 84% received concurrent chemotherapy, and 27% had preexisting cardiac disease	Nineteen patients had a grade 3 cardiac event at a median of 11 months (interquartile range, 6–24 months), and 24-month cumulative incidence was 11% (95% CI, 5% to 16%).	[19]
Dosimetric parameters for radiation pneumonitis (RP) grade 2 results of various factors between RP and non-RP patients	20 patients underwent definitive thoracic radiation. Clinical radiation RP was defined as grade ≥ 2 using the common terminology criteria for adverse events (CTCAE) v4 grading system. Equivalent doses in 2 Gy per fraction were calculated in the lung to account for differences in treatment regimens and spatial variations in lung dose (EQD2 lung)	V5 and V20 are major risk factors for radiation protection after stereotactic body radiation therapy (SBRT) treatment in lung tumor	[18]
Amifostine as a cytoprotector in radiotherapy in lung, salivary gland, bone marrow, jejunum, skin, testis, kidney, and bladder	Multicenter trial of 315 patients to receive definite or adjuvant radiotherapy with or without amifostine for head and neck cancer. In all patients, at least 75% of both parotid glands were in the radiation field. The patients were treated with daily fractions of 1.8 to 2 Gy to a total dose of 50 to 70 Gy and randomized to receive radiotherapy with or without 200 mg/m^2 amifostine IV before each fraction	Amifostine significantly reduced the incidence of moderate and severe acute xerostomia from 78% to 51%. At 1 year, the incidence of xerostomia was also significantly reduced in patients receiving amifostine Amifostine alleviates radiation toxicity in more than half of the patients with lung, head and neck, breast or uterus malignancies	[12, 41]

Table 2 (continued)

Clinical trials/studies	Patients and methods	Results and conclusion	References
Discussion on the currently available protector, WR-2721 (active in skin, intestine, marrow, mucosa, and salivary glands with lesser activity in kidney and lung and none in brain)	Phase I studies involve patients requiring palliative radiotherapy for tumors located in or adjacent to tissues which are known to be protected. They used escalating doses of WR-2721, starting at 50 mg/m^2 and will determine the maximum tolerated dose of drug, first as single doses and then as 1X, 3X, and 5X weekly for 3 and 6 weeks.	WR-2721 is not the ideal sensitizer since it did not protect all normal tissues	[42]
Dithiolethione such as oltipraz as a chemopreventive, protector against total body exposures	234 adults from the Republic of China, with hepatocellular carcinoma, were enrolled and followed in a phase II chemoprevention trial Healthy eligible individuals, including those infected with hepatitis B virus, were randomized to receive either 125 mg of oltipraz daily, 500 mg of oltipraz weekly, or placebo	A syndrome involving numbness, tingling, and pain in the extremities was associated with oltipraz intake	[43]
ACE inhibitor such as captopril, enalapril, ramipril used for the prevention of radiation-induced nephropathy, optic neuropathy, and pneumonitis	The radiation therapy oncology group has launched a phase II trial of captopril to mitigate normal lung injury in patients undergoing RT for lung cancer	ACE inhibitors could decrease the incidence of symptomatic RP among lung cancer patients	[44]
Predictive factors of symptomatic RP in primary and metastatic lung tumors treated with stereotactic ablative body radiotherapy (SABR)	59 patients with 72 primary or metastatic lung tumors treated with SABR. SABR was delivered as 45–60 Gy in 3–4 fractions, which were over 100 Gy in biological effective dose (BED) when the α/β value was assumed to be 10	The incidence of symptomatic radioprotection following SABR was acceptable with grade 2 RP being observed in most patients. Internal gross tumor volume (iGTV) over 4.21 mL and planning target volume (PTV) of over 14.35 mL were significant predictive factors related to symptomatic radioprotection	[17]

lung injury and also to better plan and administer radiation therapy [35, 36].

Conclusion and future prospects

Additional research and knowledge on radiation-related lung adverse events would have an immediate application in radiation oncology and therapeutic administration. Elucidation of the mechanisms involved in radiation-induced lung injury can offer a basis for radioprotection policies not only in the diagnostic domain but also in occupational exposure. Agents that clearly have radioprotective effects in radiation toxicity of lungs include and are not limited to natural antioxidants, current and prospective radioprotective drugs, and the mesenchymal stem cells (MSCs). For example, dietary antioxidants have been demonstrated to have potential as radioprotective agents. However, studies are unable to strongly support the protective effect. The same applies to MSCs as protective agents for both radioprotection and cure of lung injuries. Thereafter, despite the great potential of this approach in radiation-induced lung injury, a great deal of research is still required before the application of MSCs in clinical practice. Administration sites, clinical trial settings, small sample size, and patient-specific characteristics are only a few of the limiting factors while collecting and analyzing information in cancer-related studies. Nonetheless, there has been substantial progress in the field of radioprotection, especially in tailoring personalized treatments and eliminating adverse events, thus decreasing mortality rates.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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