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A Review of Clinical Radioprotection and Chemoprotection for Oral Mucositis

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Abstract

The first tenet of medicine, “*primum non nocere*” or “first, do no harm”, is not always compatible with oncological interventions e.g., chemotherapy, targeted therapy and radiation, since they commonly result in significant toxicities. One of the more frequent and serious treatment-induced toxicities is mucositis and particularly oral mucositis (OM) described as inflammation, atrophy and breakdown of the mucosa or lining of the oral cavity. The sequelae of oral mucositis (OM), which include pain, odynodysphagia, dysgeusia, decreased oral intake and systemic infection, frequently require treatment delays, interruptions and discontinuations that not only negatively impact quality of life but also tumor control and survivorship. One potential strategy to reduce or prevent the development of mucositis, for which no effective therapies exist only best supportive empirical care measures, is the administration of agents referred to as radioprotectors and/or chemoprotectors, which are intended to differentially protect normal but not malignant tissue from cytotoxicity. This limited-scope review briefly summarizes the incidence, pathogenesis, symptoms and impact on patients of OM as well as the background and mechanisms of four clinical stage radioprotectors/chemoprotectors, amifostine, palifermin, GC4419 and RRx-001, with the proven or theoretical potential to minimize the development of mucositis particularly in the treatment of head and neck cancers.

Translational Oncology (2018) 11, 771–778

Introduction

The term “Medical Machiavellianism” [1] has been coined to describe the predominant ‘first, do harm to do good’ oncologic paradigm of chemotherapy, targeted therapy and radiation administration in which toxicity and benefit are inextricably linked; by contrast, anti-Medical Machiavellianism occurs when toxicity far exceeds benefit.

A quintessential ‘anti-Medical Machiavellian’ iatrogenic toxicity, for which no established effective treatment exists and from which patients tend to suffer greatly, is mucositis and particularly oral

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Table 1. World Health Organization (WHO) Oral Mucositis Scale (modified from [10])

Grade 1 (mild)	Oral soreness, erythema
Grade 2 (moderate)	Erythema, ulcers, but oral intake not prevented
Grade 3 (severe)	Oral ulcers interfering with oral intake and requiring liquids only
Grade 4 (life-threatening)	Oral ulcers to the extent that oral alimentation is impossible

mucositis (OM), a term introduced in the late 1980s [2], involving dose-limiting inflammation and ulceration of the oral cavity during chemotherapy, targeted therapy [3], and radiation treatment [4]. While treatment-related mucositis may occur throughout the gastrointestinal tract, this review is focused on OM, which is mucositis that involves the oral cavity, oropharynx, and hypopharynx.

The debilitating sequelae of OM, which include pain, odynodysphagia, dysgeusia, dehydration, malnutrition, and systemic infection [5–7], are expensive not only in terms of the direct costs to manage them but also in terms of reduced quality of life and survival secondary to dose reduction or therapy discontinuation.

OM occurs in up to 40% of cancer patients that receive chemotherapy and approaches 100% in the treatment of head and neck cancers [8]; the symptoms, which vary in severity from Grade 1 (mild with redness and soreness) to Grade 4 (life-threatening preventing oral intake) (See Table 1), begin after a cumulative exposure to 15 Gy and worsen markedly if the total dose exceeds 60 Gy [9].

The pathogenesis of mucositis is related to direct mucosotoxicity from ionizing radiation (IR) and several anticancer agents such as methotrexate, doxorubicin, 5-fluorouracil, busulfan, bleomycin, cisplatin, carboplatin, etoposide, EGFR inhibitors, and selected tyrosine kinase inhibitors [11] in combination with infections, exacerbated by neutropenia, that develop on the damaged mucosa [12]. Methotrexate and etoposide, in particular, are secreted in saliva, which leads to an increased risk of direct mucositis [13].

While evidence of a direct causal link between mucositis and neutropenia is not definitive, the possibility that it is a contributory factor is suggested by a) reduced duration and severity of the OM with topical and systemic GM-CSF treatment (although this data is contradictory [14]) b) predisposition to mucositis with low

neutrophil counts (<400 cells/ μ L) c) high incidence of microbial infections during neutropenia since perturbation of the mucosal barrier results in a portal of entry for pathogens and neutrophil-depleted patients are less able to clear these pathogens d) recovery of the mucosa in tandem with white cell recovery, all of which implies that depletion of neutrophils leads to impaired wound healing and that neutrophil repopulation particularly during the recovery phase accelerates repair [15].

Like macrophages, neutrophils are highly plastic cells, capable of dynamically switching between two main states, N1, inflammatory, and N2, pro-repair, in a context- and time-dependent manner. Immediately following radiation exposure, neutrophils and macrophages adopt N1 and M1 activated phenotypes, respectively, in part due to the recognition and clearance of chemoradiation-induced apoptotic and necrotic cells [16], resulting in prolific expression of pro-inflammatory cytokines such as TNF and IL-6; however, as the wound matures and the dead cells, debris and pathogens are progressively cleared, the ratio of pro-inflammatory N1/M1 to pro-repair N2/M2 changes in favor of the latter, resulting in high expression levels of the anti-inflammatory cytokine, IL-10, and growth factors such as PDGF and TGF- β [17] with subsequent deposition of new extracellular matrix, reepithelialization and neovascularization. (Figure 1)

It is this time- and wound stage-dependence of macrophage and neutrophil function and polarization during the repair process, which probably accounts for the contradictory results with G-CSF (some studies show a positive effect and some no effect), since an increased influx of neutrophils and macrophages may be harmful to resolution in the earlier stages and helpful in later ones. In any case, due to these conflicting results in mucositis, the use of G-CSF is not recommended.

Traditional management of OM, which is mainly anecdotal rather than evidence-based, may consist of ice chips (oral cryotherapy), oral cavity care, multi-agent topical rinses and lozenges (e.g., Magic Mouthwash and PTA lozenges) hydration, nutritional support, systemic pain relief, low-level laser, mouth coating agents like sucralfate, growth colony stimulating factor (G-CSF) and infection surveillance and treatment. Since no single therapy or combination of therapies have been shown to be successful in OM, one strategy is to

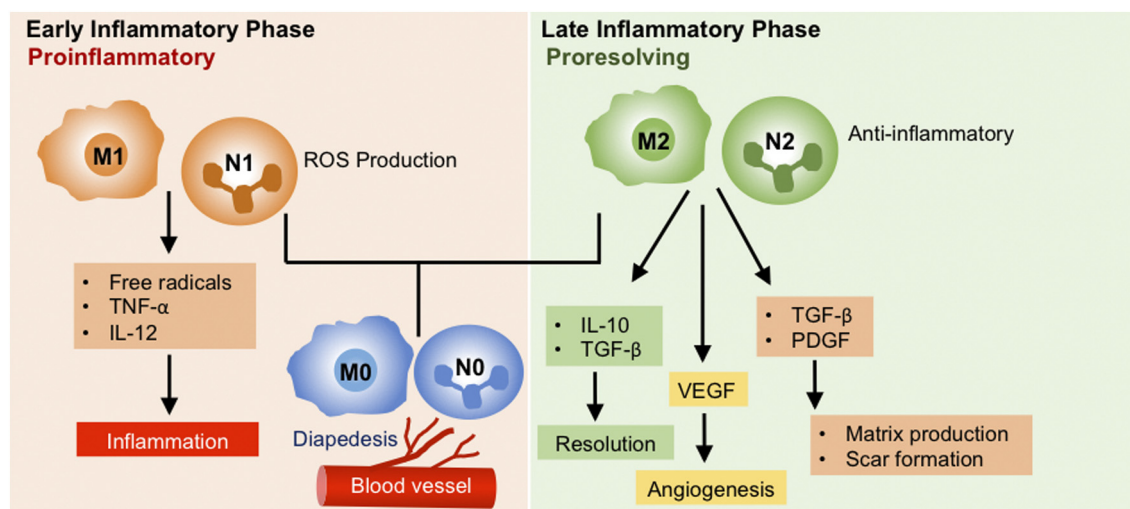
**Figure 1.** Neutrophil and Macrophage Polarization During the Early and Late Stages of Mucositis

Table 2. Risk Factors for OM

Treatment -specific	Patient -specific
Type of chemotherapy in particular 5-FU, methotrexate and etoposide	Tobacco abuse
Higher doses and continuous infusion especially with 5-FU	Neutropenia
Concomitant radiation therapy	Age
Radiation administered directly to the head and neck	Nutritional status
	Gender
	Oral health and hygiene
	Presence of dentures
	Low body mass index
	Decreased renal function
	Comorbid conditions e.g., diabetes
	Genetic polymorphisms or deficiencies in drug metabolizing enzymes
	Vitamin B12/folic acid deficiencies
	Salivary dysfunction
	Concomitant medications e.g., anticholinergics and antidepressants that decrease salivary flow
	Higher levels of oral microflora
	Previous cancer treatment
	Immune dysfunction from an underlying disease state e.g., ulcerative colitis, rheumatoid arthritis, lupus etc.
	Epigenetic factors

reduce or prevent its occurrence with chemoradioprotectors, of which there are only three with clinical data, amifostine, palifermin and RRx-001. In this review, the incidence, pathogenesis, symptoms and

impact on patients of OM are briefly summarized along with the background on these three chemoradioprotectors and the proposed mechanisms for their beneficial effects.

Incidence and Risk Factors of OM

In general, while mucositis occurs in up to 40% of patients treated with conventional chemotherapy, more than 70% of patients that undergo conditioning therapy for bone marrow transplantation [18] and virtually all head and neck patients that receive simultaneous radiochemotherapy [19], its severity is highly variable and depends on treatment- and patient-specific risk factors (see Table 2). Of the two, treatment-related risk factors, which include dose, location, duration of chemotherapy, and concomitant use of chemotherapy and radiation, are the more impactful; however, since several patient-specific risk factors are potentially modifiable through preventative actions (e.g., poor oral hygiene, the presence of dental appliances, diabetes, oral lesions, malnutrition, neutropenia, folic acid/vitamin B12 deficiencies, concomitant medications, salivary hypofunction/xerostomia [20], tobacco use etc.) they should be identified and addressed before the start of therapy by both an oncologist and a dentist. Other less modifiable patient risk factors include age, gender, body mass index, underlying immune dysfunction, polymorphisms and deficiencies in drug metabolizing enzymes and other epigenetic and genetic factors, which affect the expression or activity of cytokines and transcription factors, such as TGF-β, NF-κB and p53 and genes such as COX-2 and MMPs, all of which are implicated in the development of mucositis [21].

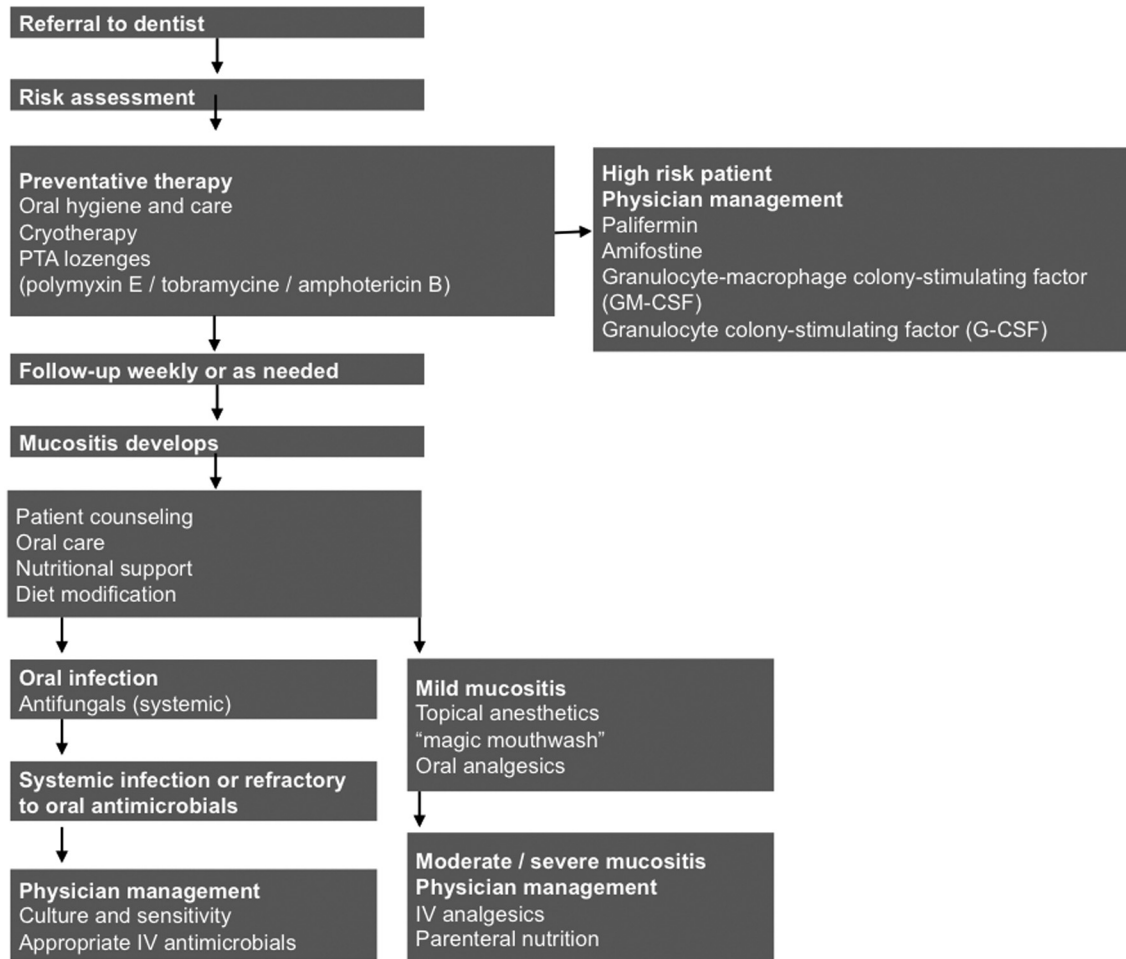


Figure 2. Flow chart of management Adapted from Napenas [64]

Adverse Impact on Patient Outcomes and Quality of Life

While treatment-related nausea, vomiting and cytopenias are the most common adverse events in oncology, mucositis has emerged as the most significant according to an NCCN task force [22]. Its adverse physical, social and psychological impacts on patients are legion and include the need for total parenteral nutrition (TPN), higher risk of systemic infections, increased use of antifungals and opioid analgesics, increased hospitalizations with longer hospital stays, social isolation and depression due to the inability to talk and eat, subsequent dose reductions, treatment interruptions and discontinuations, and as a corollary to dose reductions and treatment interruptions/discontinuations, diminished antitumor responses and shorter survival. The economic consequences are far from trivial as well with the incremental cost exceeding \$17,000 (USD) for patients with head and neck cancer [23].

The cornerstone of management for the substantial pain and ulceration, which results and which may persist even after treatment is completed, are parenteral opioid analgesics that themselves carry the inherent risk of aversive side effects such as constipation and decreased alertness [24]. (Figure 2)

Pathogenesis

The pathogenesis of oral mucositis is thought to involve direct and indirect mechanisms resulting from treatment with chemotherapy and/or radiotherapy that interfere with the division and maturation of epithelial cells.

a) Direct Mechanisms

The epithelial cells of the oral mucosa have a fast turnover rate, usually every 7 to 14 days, which explains their direct susceptibility to apoptosis from cytotoxic therapy and the onset of mucositis approximately two weeks after chemotherapy initiation [25,26].

b) Indirect Mechanisms

Indirect toxic bystander effects that exacerbate the morbidity of mucositis include the release of pro-inflammatory mediators such as tumor necrosis factor (TNF), interleukin-1 beta (IL-1 β) and IL-6 from activated M1 and N1 macrophages and neutrophils, with a concomitant decrease in the anti-inflammatory cytokines IL-10 and TGF- β that would normally act to dampen the inflammatory response as well as secondary infection/colonization from/by Gram-negative bacteria and fungal species. Oral infections also tend to coincide with neutropenia.

Sonis has proposed a 5-stage model of mucositis, the importance of which is that, while likely incomplete, it identifies potential therapeutic targets (e.g. free radicals, pro-inflammatory cytokines, infection) that could hinder or reverse the development of OM with radio- and chemoprotectors. (See Table 3 and Figure 3)

Amifostine

a) Background

Initially under the auspices of the Manhattan Project during World War II, a systematic screen of 4400 compounds was undertaken at Walter Reed Army Research Institute to identify potential radio-protectors, which culminated in the selection of WR-27213 (the "WR" signifies Walter Reed) or Amifostine on the basis of its superior

Table 3. The 5-phases of Oral Mucositis Adapted from Sonis [27]

Phase I—Initiation	Chemotherapy or radiation-induced reactive oxygen species (ROS) and lipid peroxidation results in DNA damage, release of pathogen-associated molecular pattern (PAMP) and damage-associated molecular pattern molecules (DAMPs) and cellular apoptosis
Phase II—Signaling	ROS stimulate the NF- κ B pathway, which induces production of proinflammatory cytokines (TNF- α , IL-1 β , IL-6)
Phase III – Amplification	Proinflammatory cytokines trigger tissue injury, apoptosis, vascular permeability, and activation of cyclooxygenase-2
Phase IV—Ulceration	Ulceration occurs, which serves as a portal of entry for microorganisms. The presence of bacteria activate macrophages and neutrophils to further produce proinflammatory cytokines
Phase V—Healing	Signaling from the submucosa promotes epithelial migration, proliferation and differentiation

activity and safety profile [28]. Renamed Ethyol after its acquisition by MedImmune who later sold it to Astra Zeneca and now marketed by Clinigen Group, a UK pharma company, as well as two generic companies, Sun Pharma and Mylan Pharmaceuticals, amifostine has been used and approved clinically to ameliorate the side effects of chemotherapy and radiotherapy. Of the two FDA approvals, the first was in 1996 to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small cell lung cancer; the second was in 1999 for radiation-induced xerostomia in Head and Neck cancer [29]. Reportedly, amifostine was provided to the Apollo astronauts on their trip to the Moon in case of exposure to solar flare radiation [30].

b) Mechanism and Toxicities

A phosphorylated aminothioliol prodrug [31], amifostine is dephosphorylated by the enzyme, alkaline phosphatase that is at high levels in normal tissues but at low levels in tumors and thus converted to its active free radical-scavenging sulfhydryl metabolite, WR-1065, which provides a selective mechanism for protection of non-CNS tissues (since amifostine does not cross the blood brain barrier). Other mechanisms for preferential protection of normal tissues include increased uptake in the salivary glands and kidneys. As a free radical scavenger, amifostine quenches DNA damaging species from ionizing radiation and alkylating agents. (Figure 4) However, in animal studies it was observed that amifostine diffuses into malignant tissues [32], albeit more slowly than normal tissues, which raises a still-lingering question mark, even nearly 30 years after its approval, about the potential of amifostine to also protect tumors from radiation and chemotherapy cytotoxicity. In addition to this potential for tumor cytoprotection, its use in the clinic is limited by severe toxicities such as emesis and hypotension.

Palifermin

a) Background

Palifermin or Kepivance is a recombinant human form of Keratinocyte growth factor (KGF) originally derived from embryonic lung fibroblasts and developed by Amgen that acts specifically on the differentiation, proliferation and survival of epithelial cells, which express the KGF receptor, throughout the GI tract [33]. In 2004, the FDA approved the use of palifermin [34] to reduce the incidence and duration of severe oral mucositis in patients with hematological malignancies [35]. However, palifermin has not been approved for use in head and neck cancers likely due a lack of improvement in

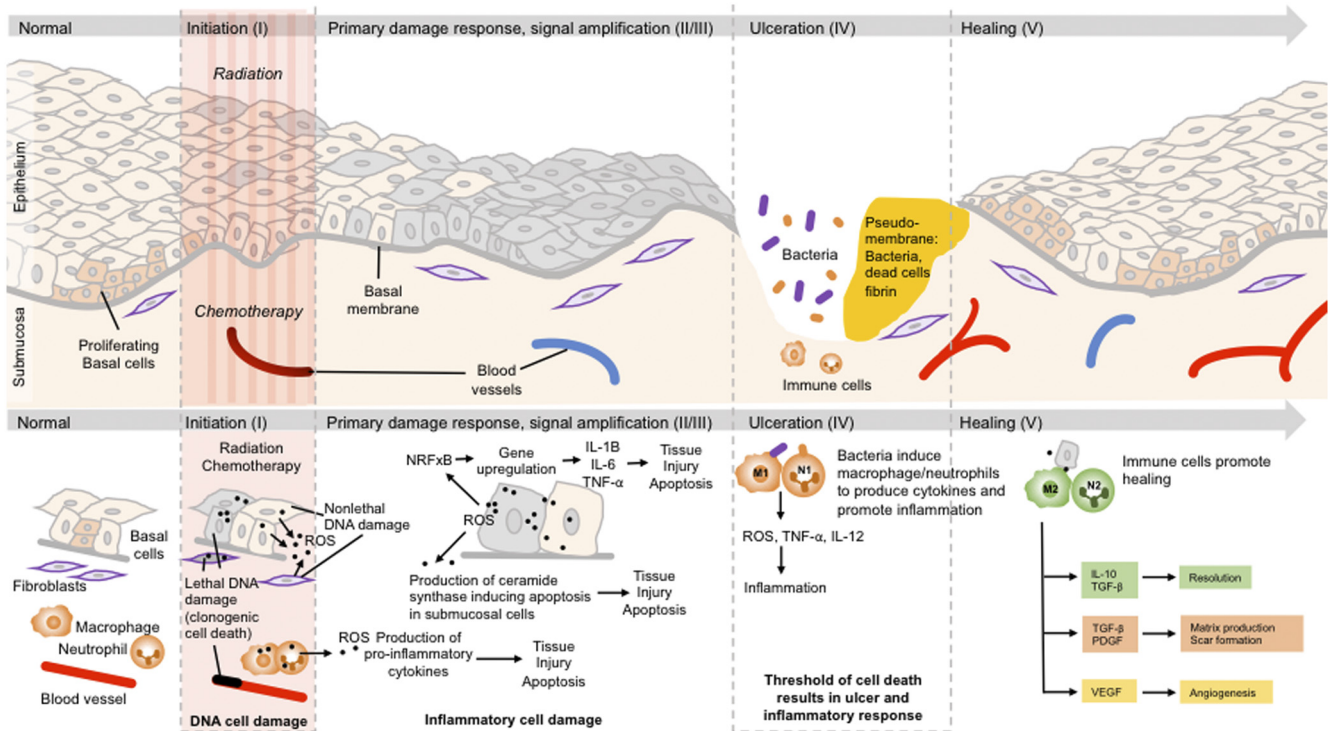


Figure 3. Illustration of the 5 phases of mucositis adapted from Sonis [65]

narcotic use, patient-reported pain, or chemoradiotherapy compliance despite a significant reduction in the severity and duration of oral mucositis [36,37].

b) Mechanism and Toxicities

Palifermin binds to the KGF receptor [38], which induces the differentiation of epithelial cells and mediates a host of biological effects including upregulation of Th2 cytokines, inhibition of epithelial cell apoptosis, prevention of DNA strand breaks and tissue remodeling [39].

While the FDA package insert [40] states under its Warnings and Precautions section that palifermin is associated with the proliferation of KGF-receptor bearing malignant cells as well as secondary cancers in laboratory animals, a long term follow up of 672 patients treated with palifermin or placebo (428 palifermin and 244 placebo) with a median follow-up time of 7.9 years demonstrated no differences in the incidence of secondary malignancies [41]. Palifermin is generally well tolerated with mild-to-moderate adverse events of the skin and the mouth [42].

GC4419

a) Background

Excessive formation of reactive oxygen species such as superoxide (SO) radical O_2^- plays a central role in the pathogenesis of mucositis. The antioxidant enzyme superoxide dismutase (SOD) detoxifies superoxides via transformation to the relatively stable and poorly reactive oxidant, hydrogen peroxide (H_2O_2). However, during radiation therapy, the overproduction of superoxide radicals so overwhelms native SOD enzymes that SO-mediated damage results, which suggest that exogenous administration of superoxide dismutase, will reduce the toxicity of radiation and chemotherapy. Indeed, during the 1970s, Orgotein, a Cu-Zn superoxide dismutase, was used successfully to ameliorate radiation-induced toxicity in bladder tumors [43]. However, use of SODs in the clinic has been limited by problems of immunogenicity when derived from non-human sources, large size (MW ~30,000) [44] and a short half-life, since they are prone to hydrolysis *in vivo*, and therefore require continuous infusion [45].

As an alternative to these large unstable immunogenic proteins, synthetic small molecule SOD mimetics (SODm) have been developed. One example of a non-peptide SODm is GC4419, a manganese-based low molecular weight small molecule that selectively dismutates superoxide anions but not other biologically relevant oxidizing species

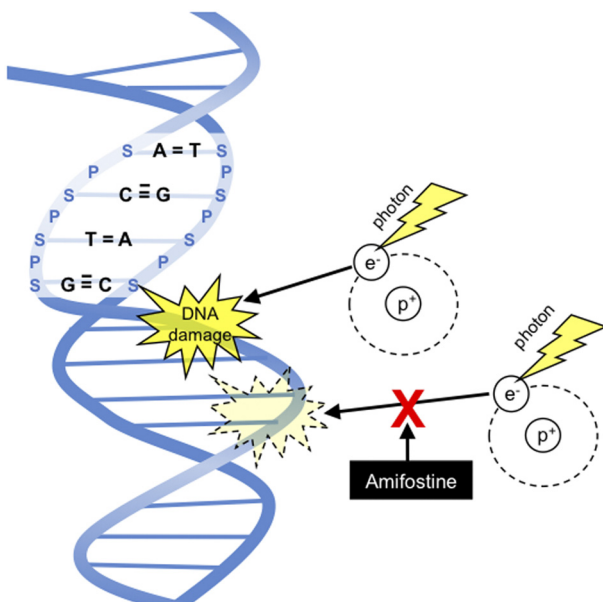


Figure 4. Amifostine as a thiol-based free radical scavenger, which prevents DNA damage

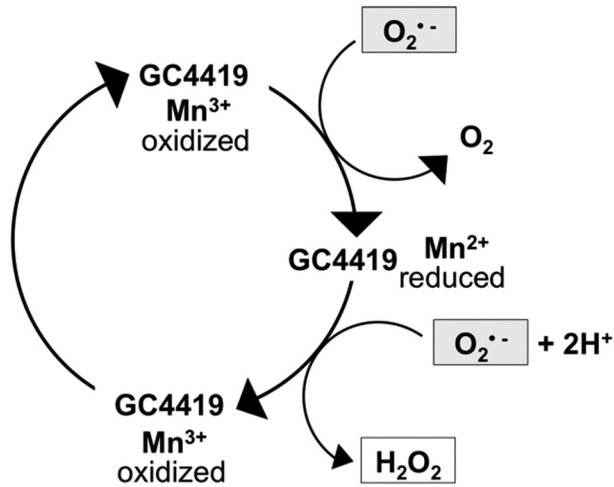


Figure 5. Redox cycling of the catalytic metal, Mn, in GC4419

from Galera Therapeutics, Inc. In a recently completed a multi-site phase 2b clinical trial with 223 head and neck cancer patients, GC4419 resulted in a 92% reduction in the duration of oral mucositis ($P = 0.024$) and has received FDA fast track designation [46].

b) Mechanism and Toxicities

The selectivity of GC4419 for superoxide is due to the reduced manganese (II) ion in the center of the molecule, which is alternately reduced by superoxide anion to Mn (III) and re-oxidized to Mn (II) by protonated superoxide via a one-electron pathway. Superoxide is the only kinetically competent oxidant/reductant in the redox cycle of Mn: Other one-electron radicals such as nitric oxide and oxygen are too sluggish to oxidize Mn (II) while the more potent peroxyxynitrite, hydrogen peroxide and hypochlorite, which transfer two electrons, are not able to oxidize it [47]. (Figure 5)

In a Phase 1b/2a trial of GC4419 a maximum tolerated dose was not reached and only two dose-limiting toxicities, grade 3 gastroenteritis and vomiting with hyponatremia, were observed [48].

One potential “toxicity” of GC4419 and all SOD mimetics is tumor protection since antioxidants like SOD inhibit the formation of free radicals, which are cytotoxic. However, because GC4419 selectively dismutates superoxide into H_2O_2 , which is an oxidant in its own right, tumor inhibition is more likely than tumor protection.

RRx-001

a) Background

Similar to amifostine, RRx-001 also originated in a military setting, having been derived from 1,3,3-Trinitroazetidine or TNAZ, a melt cast explosive [49]. Developed by EpicentRx, a San Diego, California-based biotech, RRx-001 is under investigation in a Phase II clinical trial called QUADRUPLE THREAT (NCT02489903) as a chemosensitizer of platinum resistant/refractory small cell carcinoma and a high-grade neuroendocrine carcinoma and as a radioprotector in case of nuclear emergency at the Armed Forces Radiobiologic Research Institute (AFRRI). Preliminary data from the QUADRUPLE THREAT trial indicate that in 24 enrolled patients RRx-001 was associated with 4.2% of Grade 3/4 neutropenia (1/24) and a 0% rate of febrile neutropenia compared to a historical rate of neutropenia of 79.8% [50] and an 11% rate of febrile neutropenia for platinum plus etoposide, which may be indicative of bone marrow chemoprotection. Preclinical data also provide evidence of radioprotection [51] and platinum chemoprotection [52]. A Phase II proof of concept randomized chemoradioprotection trial for oral mucositis in head and neck cancer is in preparation and scheduled to start at end of 2017 with three weekly doses of RRx-001 preceding the start of cisplatin and radiotherapy (RT) and continued RRx-001 dosing during platinum + RT rest periods.

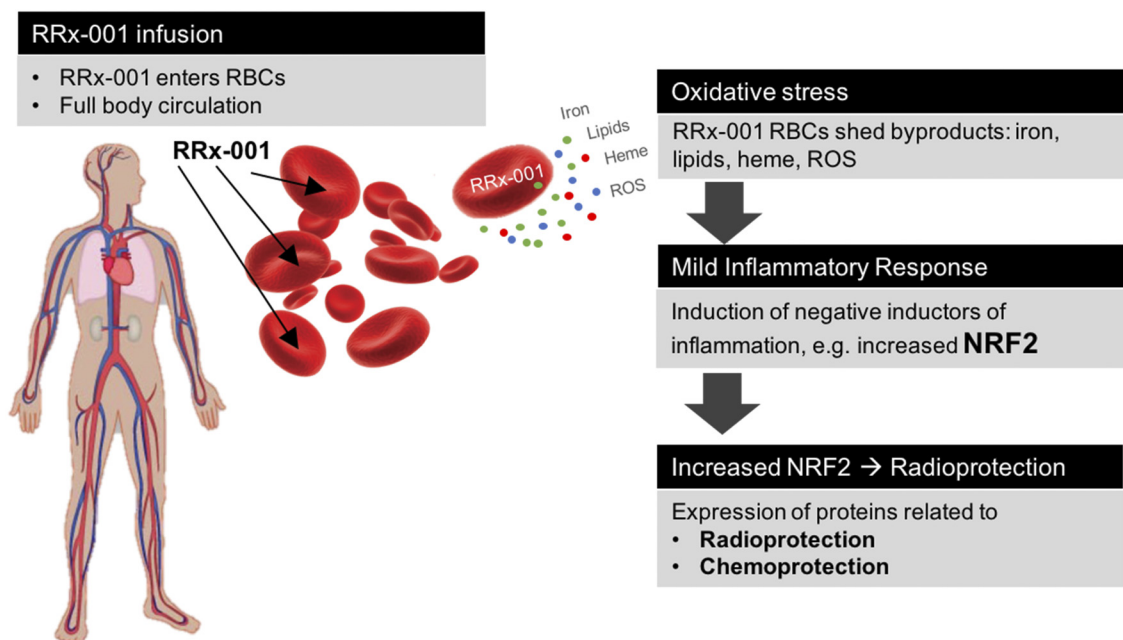


Figure 6. Schema of RRx-001-mediated oxidative preconditioning, resulting in potential chemoprotection and radioprotection

b) Mechanism and Toxicities

The mechanism of chemoradioprotection is red blood cell-based, since RRx-001 binds to and oxidatively modifies hemoglobin (Hb). The result of Hb oxidation is deposition of iron and heme in the red blood cell membrane with subsequent shedding of iron and lipid-laden microvesicles in normal tissues as an RBC self-protection mechanism against reactive oxygen species (ROS) accumulation. The deposition of these Fenton-active microvesicles in healthy tissues such as the bone marrow end induces a slight oxidative stress, which results in upregulation of Nrf2-dependent antioxidant enzymes [53]. Similar to ischemic preconditioning, first described in the dog myocardium [54], whereby periods of ischemia and reperfusion prior to a prolonged period of ischemia dramatically increases ischemic tolerance in solid organs such as the heart, liver, kidney, and bones, this form of RRx-001-mediated *oxidative* priming to induce the endogenous Nrf2 antioxidant machinery in normal cells preconditions them to better withstand subsequent oxidative insults. As both a single agent and in combination with radiation and chemotherapy, RRx-001 is well tolerated and to date has not been associated with any dose-limiting toxicities in over 200 treated patients [55]. (Figure 6)

Conclusion and Possible Future Directions

According to Sonis' characterization, on whose model the current 5 step pathogenesis of OM is based, mucositis is a toxicity that "largely defies effective intervention" [56]. In light of the lack of progress to treat it despite an extended clinical legacy, which reaches as far back as Marie Curie's discovery of radium in 1897 [8], and on the premise that an ounce of prevention is worth a pound of cure, a chemo- and radioprotection strategy would seem to make eminent sense.

Unfortunately, as a field, radio- and chemoprotection also carries a lot of historical baggage, since its inception approximately 7 decades ago, when the amino acid cysteine was identified as a putative radioprotector in 1949 [57]. In all of this time, despite multiple potential candidates, including antioxidants, plant extracts, antihypertensives, steroid hormones, statins and cytokines [58], many of which have failed in clinical trials due to acute toxicities [59,60], the only one to be approved as both a chemo- and radioprotector is amifostine [61]; however, its reputation and, by extension the whole chemo- and radioprotection field of which amifostine serves as the prototype and standard bearer, has suffered by virtue of its multiple toxicities including nausea, vomiting and hypotension, underwhelming clinical outcomes and the still-lingering possibility, to date never absolutely disproven, that amifostine also protects tumors and reduces therapeutic gain [62].

Hence, these black marks on amifostine and the resultant shortfall of candidates in clinical evaluation contribute to the impression that chemoradioprotection is a therapeutic and commercial dead-end, which, in turn, disincentivizes R&D and serves to establish a vicious cycle of disinterest and disinvestment. However, the magnitude of the unmet need in mucositis, absence of competition and potential market of at least 500,000 plus patients per year [63], which is the annual worldwide incidence of head and neck (H&N) cancer, since almost all H&N patients receive loco-regional radiotherapy also presents a high-reward opportunity for private sector investors e.g., pharmaceutical companies and venture capital firms. In addition to H&N cancer, a market also exists for patients treated with commonly prescribed chemotherapeutic agents that are associated with mucositis such as methotrexate, doxorubicin, 5-fluorouracil, etoposide, cisplatin, and carboplatin.

In terms of future directions, one potential strategy is to treat with a cocktail of RRx-001, amifostine, palifermin, CG4419, which has shown promise in the clinic, and potentially other agents as well such as corticosteroids and hematopoietic factors on the premise that they may act synergistically to protect normal tissues given their non-overlapping mechanisms of action. Moreover, RRx-001, as a chemoprotector as well as a radioprotector, may attenuate the dose-limiting toxicities of amifostine. If successful, and anticancer activity is not adversely affected, the immediate result will likely be a paradigm shift from *quantity* of life to *quality* of life-centered treatment where the same regimens are given with the same or better efficacy but with considerably less toxicity.

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