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Novel drugs to ameliorate gastro-intestinal normal tissue radiation toxicity in clinical practice: what is emerging from the laboratory

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Abstract

Purpose of the review—To give an overview of promising novel agents under development for the prevention and reduction of gastro-intestinal radiation injury.

Recent findings—Currently, several novel agents are being tested as drugs to prevent or reduce gastro-intestinal radiation injury. These drugs may not only prevent injury, but may also mitigate toxicity, i.e. reduce injury after radiation exposure has occurred. Promising novel agents include the somatostatin analogue SOM230, growth factors, agents acting on the toll-like receptor 5 pathway, endothelial protectants, and the vitamin E analogue γ-tocotrienol.

Summary—Gastro-intestinal radiation injury is the most important dose limiting factor during radiotherapy of the abdomen or pelvis. It may severely affect quality of life both during radiotherapy treatment and in cancer survivors. To date, there are no agents that can prevent or reduce intestinal radiation injury. Hence, there is an urgent need for the development of novel drugs to ameliorate intestinal toxicity during and after radiotherapy. This review summarizes several agents that have been shown to reduce intestinal radiation injury in animals. Further research is needed to investigate their safety and efficacy in patients receiving radiotherapy for abdominal or pelvic tumours.

Keywords

radiation injuries; radioprotection; somatostatin; growth factors; toll-like receptor; γ-tocotrienol

Introduction

Radiotherapy plays a crucial role in the treatment of various cancers. Depending on the tumour site it is either delivered before or after surgery or as a definitive treatment. Even though novel technical advances in treatment delivery have enabled more selective irradiation of the region of interest or tumour, normal tissue radiation toxicity remains the most important dose limiting factor of radiotherapy. Injury to the gastro-intestinal tract is oft the most important cause of radiation-induced side effects in patients being treated for abdominal and pelvic tumours.

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Symptoms of intestinal radiation injury may occur during and/or after treatment. Depending on the time of onset intestinal radiation injury is divided into acute and chronic injury. Acute radiation toxicity occurs during and shortly after the treatment period. It may affect quality of life during treatment and may even require treatment interruption or alteration. The most important symptoms of acute gastro-intestinal toxicity include: diarrhoea, nausea, increased stool frequency, bleeding, abdominal and rectal/anal pain, decreased food uptake, and fluid and electrolyte loss. The severity of the symptoms may vary from mild discomfort to severely disabling and requiring hospital admission.

Chronic intestinal radiation injury is generally defined as injury present or occurring at least 3 months after treatment. The latency period of chronic radiation toxicity may be months up to years. Chronic gastro-intestinal injury may reduce quality of life in long term cancer survivors. Again the symptoms are various, including change in bowel habit, diarrhoea, faecal incontinence, pain, and intestinal blood loss.

In contrast to the earlier belief that acute and chronic injury are two unrelated phenomena, it now has been recognized that part of the chronic effects is consequential to early toxicity.

Cancer patients could greatly benefit from pharmacological agents that are able to prevent or reduce gastro-intestinal radiation injury. Unfortunately, to date, there are no effective pharmacological interventions to prevent the development of gastro-intestinal radiation toxicity after abdominal or pelvic irradiation. There is some evidence from phase I and II trials that the thiol-containing compound amifostine may reduce rectum toxicity when either administered systemically or topically. However, in contrast to head and neck cancer, the usefulness of amifostine in radiotherapy for abdominal or pelvic cancer has not been confirmed in a phase III trial [1–4]. Moreover, systemic amifostine treatment may cause severe side effects [5]. Therefore, the use of amifostine is not widely implemented in clinical practice. Currently, intestinal radiation toxicity can only be managed symptomatically with analgesic, anti-emetic agents or drugs to reduce diarrhoea.

Hence, novel substances that can prevent or reduce intestinal radiation injury in cancer patients are urgently needed. During the last few years it is become clear that these agent do not necessarily need to be radioprotectants, i.e. agents administered before radiation exposure that protect the cell at the moment of exposure. Agents may also reduce radiation injury by targeting pathways more downstream in the pathogenesis of radiation injury [6**]. Administration of these substances may be started after radiation exposure. These agents are called radiation mitigators opposed to protectants. Recently, various novel target pathways to mitigate radiation injury have been discovered.

Remarkably, many of the recently indentified candidate agents to reduce radiation injury were initially not investigated to reduce radiation injury in cancer patients, but to reduce toxicity after radiation exposure in non-clinical situations. Lately, the socio-political climate has been supportive towards research programmes to develop novel radiation countermeasures for emergency situations such as nuclear accidents and terrorist attacks with radioactive material. This trend has not only provided novel opportunities and funds to develop interventions for non-clinical radiation exposure, but may also benefit cancer treatment. The newly discovered drug may develop as “dual utility” drugs that can both be used as radiation countermeasure and in patients undergoing radiotherapy. The field of radiotherapy may therefore benefit from novel advances made in the development radiation countermeasures.

This review will discuss several promising novel drugs emerging from the lab that that may be able to prevent or reduce intestinal radiation injury in cancer patient. The discussed

agents appear to exert their effect by protection or stimulation of the intestinal epithelium, endothelium or immune system.

Somatostatin analogues

Somatostatin analogues can ameliorate intestinal radiation by preventing post-irradiation pancreatic enzyme-dependent intestinal auto-digestion. Radiation exposure causes breakdown of the intestinal epithelial barrier due to a decrease in intestinal crypt/stem cell proliferation and inadequate cell supplies to compensate for continuous enterocyte loss. As a result, subepithelial tissues may be exposed to intraluminal pancreatic enzymes that subsequently aggravate the injury by initiating auto-digestion of the intestine and the induction of inflammatory processes [7]. Strategies to reduce exogenous pancreatic secretion, like pharmacological inhibition with somatostatin analogues, have been shown effective in reducing intestinal radiation toxicity in animals.

Somatostatin analogues are already in clinical use for other indications like the treatment of neuroendocrine tumours and diarrhoeal syndromes [8]. Various animal studies have confirmed that treatment with the somatostatin analogue octreotide reduces intestinal radiation injury [9;10]. Human studies investigating the effect of octreotide on post-irradiation diarrhoea in patients being treated for rectal or anal cancer have shown mixed results [11;12]. The fact that the studies only showed a modest or even no effect of octreotide might depend on the limited volume of small intestine, the site where somatostatin analogues are expected to exert their effect, in the radiation field.

The recently developed somatostatin analogue SOM230 (Pasireotide) may be more effective in reducing radiation injury than octreotide. It has a more favourable pharmacokinetic profile and broader receptor affinity. Human subject studies have shown that SOM230 is well tolerated [13]. Animal studies with SOM230 have shown that SOM230 reduces acute intestinal radiation injury by mechanisms depending on inhibition of pancreatic enzyme secretion [14]. SOM230 was not only effective when started before radiation exposure, but even reduced radiation toxicity when started up to 48 hours after exposure [15*].

At this moment, little is known a about the effect of SOM230 on tumour cell survival during radiotherapy. However, since SOM230 appears not to act as a cytoprotector, but to preserve the intestinal mucosa by reducing pancreatic enzyme secretion, it seems to be unlikely that SOM230 would protect tumour cells during radiotherapy. In fact, SOM230 may reduce tumour growth by itself by inhibiting IGF-1 and VEGF secretion [16;17]. Hence, SOM230 appears be an attractive agent to reduce intestinal radiotoxicity during radiotherapy. SOM230 may be able to improve the therapeutic index of radiotherapy treatments in which the intestine, especially the small intestine, is in the radiation field. Phase I and II studies are needed to determine the safety and potential efficacy of SOM230 in abdominal and pelvic radiotherapy.

Growth factors and growth factor-like agents

The use of growth factors and growth factor-like agents to improve post-irradiation intestinal epithelial recovery has been a popular research focus for several years. Various agents have been tested in this respect. Over the years, glucagon-like peptide 2 as well as keratinocyte and fibroblast growth factors have been shown to ameliorate post-irradiation intestinal injury in various animal models [18–23]. Moreover, recently, recombinant human epidermal growth factor as well as R-spondin 1, an intestinal stem cell growth factor, were shown to reduce apoptosis and improve recovery of the intestinal villi [24;25]. These growth factors appear to exert their effect trough inhibition of PUMA-dependent apoptosis and induction of Wnt-β-catenin regeneration [25;26].

Growth factor-like agents may be used to reduce radiation injury as well. For example, the growth factor-like lipid mediator lysophosphatidic acid (LPA) was shown to reduce post-irradiation intestinal apoptosis through the LPA receptor 2 subtype [27].

In the above mentioned animal studies, the growth factors did not appear to affect the effects of radiation on tumours. However, further research is needed to confirm these results. If used to reduce acute radiation toxicity, it is almost inevitable to administer the drugs during the radiation course. Only growth factors that do not affect radiation-induced tumour cell kill, tumour growth or other malignant tumour properties can be considered for clinical use.

Agents acting on the Toll-like receptor 5 pathway

Toll-like receptors (TLR) are an important component of the intestinal innate immunity. Activation of TLRs by commensal microflora is essential for the protection against intestinal injury and in the regulation of epithelial repair [28;29]. Activation of TLRs reduces the sensitivity of enterocytes to radiation-induced apoptosis. The bacterial protein flagellin is a natural agonist of toll-like receptor 5 (TLR5). Both flagellin and the less toxic synthetic flagellin derivate CBLB502 have been shown to be potent radioprotectors in both mice and non-human primates [30;31].

Pretreatment with Toll-like receptor 5 agonist prevents radiation-induced apoptosis of intestinal epithelial cells and subsequent injury. The c-jun N-terminal kinase (JNK) as well as nuclear factor κβ (NF-κβ) have been identified as pathways through which flagellin reduces radiation-induced enterocyte apoptosis [31;32*].

A concern regarding the use of TLR5 receptor agonist is the possible induction of systemic inflammation. TLR5 receptor agonist can only be considered for clinical radioprotection if they do not induce effect degrading toxicity [33]. In order to increase the specificity of the therapy it might be necessary to use agents that act more downstream in the TLR5 receptor pathway than TRL5 receptor agonist. One of the candidate molecules is the mitogen-activated protein kinase phosphatase-7 (MKP-7) [32]. TLR5 activation upregulates the transcription of MKP-7 and MKP-7 has already been shown to limit post-irradiation injury.

Further research is needed to determine the safety and efficacy of the above mentioned agents before they can be used clinically to prevent intestinal radiation injury.

Endothelial protectants

Strategies that reduce radiation-induced microvascular endothelial cell apoptosis or endothelial dysfunction may be able to prevent intestinal radiation injury [34]. Although under debate [35–37], it is generally believed that post-irradiation endothelial apoptosis contributes to intestinal stem cell dysfunction and mucosal injury [34]. The sphingolipid ceramide has been shown to play a crucial role in radiation-induced endothelial apoptosis. Radiation exposure can cause hydrolysis of cell membrane sphingomyelin by acid sphingomyelase which results in the formation of ceramide. Ceramide then initiates the apoptotic process via the mitochondrial system [38]. Bonnaud et al. showed that inhibition of post-irradiation ceramide production promotes post-irradiation endothelial survival and ameliorates intestinal injury in mice [39*].

Not only reducing endothelial apoptosis, but also improving post-irradiation endothelial function with agents like 3-hydroxy-3-methyl-glutaryl-CoA (MHG-CoA) reductase inhibitors has been shown to reduce intestinal radiation injury in animal models [40;41].

Additional studies are needed before these strategies can be translated to the clinic.

γ-Tocotrienol

One of the other promising new agents to reduce intestinal radiation injury in mice is the vitamin E analogue γ-tocotrienol. Vitamin E analogues or so called tocols are powerful antioxidants with favourable toxicity profiles. Hence, they are interesting candidates for the development of radioprotectants.

Recently, it has become clear that there are remarkable differences in radioprotective potential among the various tocols. In the past, most studies on the effect of vitamin E on radiation toxicity were performed with α-tocopherol. α-Tocopherol is the most abundant isoform and the most widely used vitamin E supplement [42–48]. Several animal studies have now shown that other isoforms of vitamin E are more effective in ameliorating the acute radiation toxicity [49]. Especially γ-tocotrienol appears to be a powerful radioprotectant.

A single dose of γ-tocotrienol administered before radiation exposure has been shown to decrease radiation injury in several organ systems, including the intestine, the hematopoietic system and the vascular system [50;51].

With respect to the gastrointestinal syndrome, γ-tocotrienol significantly improved intestinal crypt cell survival as well as the post-irradiation recovery of the intestinal mucosal surface area. Moreover, considering the importance of vascular injury and the immune system in the development of intestinal radiation injury, the effects of γ-tocotrienol on these systems may indirectly affect the intestinal system.

γ-Tocotrienol may be so efficient in reducing intestinal radiation injury because tocotrienols accumulate in de small intestine and colon to a higher levels than tocopherols supplemented in the same concentration [52]. Other properties that may contribute to the powerful radioprotective effects of γ-tocotrienol are its ability to concentrate in endothelial cells to levels that are 30–50 fold greater compared to α-tocopherol and to inhibit the enzyme MHG-CoA reductase [53;54]

In order to develop as a therapy to reduce radiation injury in patients undergoing radiotherapy, γ-tocotrienol should not protect the tumour and should be safe to be used in humans. To date little is known about the effects of γ-tocotrienol on tumour cells during radiotherapy. γ-Tocotrienol may sensitize tumour cells to radiation exposure and chemotherapeutic agents [55–57], however, further studies are needed to confirm that γ-tocotrienol does not protect tumour cells against radiation. With regard to the safety of γ-tocotrienol in human beings, studies form other fields have shown that γ-tocotrienol supplementation is well tolerated in human subjects [58;59].

Final remarks and conclusion

During the last few years several new agents have been shown to ameliorate intestinal radiation injury in animal models. Interestingly, some of these agents do not only prevent injury, but also mitigate injury when administration is started after radiation exposure.

Further research is needed to investigate the safety and efficacy of these newly discovered drugs in patients undergoing radiotherapy. Importantly, protective or mitigating agents can only be considered for clinical use if they are proven not to hamper the anti-tumour effect of the radiotherapy treatment.

With regard to the efficacy, it is crucial that both the effects on acute and late intestinal radiation injury are assessed. Even though late injury may be consequential to acute toxicity,

it is possible that certain agents are more effective against early toxicity than late injury and vice versa. In order to improve the quality of life of cancer patients both agents that reduce acute and late injury are needed.

Altogether, several promising radioprotectants and mitigating agents have emerged from the lab. These agents include SOM230, growth factors, agent acting on the TLR5 pathway, endothelial protectants, and γ-tocotrienol. Now the work should be continued and the clinical applicability and efficacy of these agents should be investigated.

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Key points

- There is an urgent need for novel agents to prevent and/or reduce intestinal gastro-intestinal radiation injury in patients being treated for abdominal and pelvic tumours.
- Promising novel radioprophylactic and mitigating agents include the somatostatin analogue SOM230, growth factors, agents acting on the toll-like receptor 5 pathway, endothelial protectants, and the vitamin E analogue γ-tocotrienol.
- Before these newly discovered drugs can be clinically implemented, further research is needed to establish their safety and efficacy in reducing both acute and chronic gastrointestinal radiation injury in patients.