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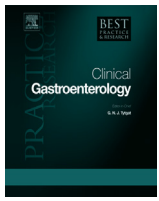

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Management of radiation and chemotherapy related acute toxicity in gastrointestinal cancer

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A B S T R A C T

Possible toxic effects following radiation and chemotherapy of gastrointestinal tumours may cause a depletion of the mucosal barrier within the radiation volumes with severe mucositis. Diarrhoea, nausea, emesis and severe malabsorption followed by infections with dehydration and electrolyte disorders have to be encountered. For prevention and treatment of oropharyngeal mucositis an oral care protocol, oral cryotherapy together with benzydamine mouthwash may be recommended. Lower gastrointestinal diarrhoea is best treated by Octreotide (>100 μg s.c. bid) if loperamide is ineffective and amifostine (340 mg/m^2 IV) to prevent radiation proctitis.
Enteral nutrition may be necessary with severe malnutrition or no enteral food intake for >7days or insufficient intake (<60%) for >10 days. With severe generalized mucositis or severe radiation induced enteritis parenteral nutrition will be initiated. Following the application of highly emetogenic chemotherapy regimen, 5-HT3 antagonists, dexamethasone and aprepitant, whereas in moderate risk levels 5-HT3 antagonist plus dexamethasone may be sufficient.

Introduction

Concurrent application of ionizing radiation and chemotherapy for different cancer sites of the gastrointestinal tract has recently emerged as a highly effective treatment option and is regarded as the

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major progress in clinical oncology of the last two decades. Advances in terms of improved survival alongside with better quality of life have been demonstrated on a high-evidence level for squamous cell carcinoma of the oesophagus, adenocarcinoma of the oesophago-gastric junction [1], carcinoma of the stomach [2], as well as rectal cancer [6], albeit to a lesser extent for pancreatic cancer [3–5]. This progress was only possible with a better understanding and improved preventive and treatment measures of acute toxic effects that almost invariably will occur during and after chemoradiation. In fact, side effects will appear to be even more pronounced when combining two treatment modalities at the same time compared to a sequential approach that has been the standard treatment before.

A complex network of possible toxic effects (see Fig. 1) following radiation and chemotherapy has to be contemplated when treating patients with gastrointestinal tumours. Ionizing radiation will cause a substantial depletion of the mucosal barrier within the radiation volumes that may eventually lead to severe mucositis particularly with the application of concurrent chemotherapy. As possible consequences diarrhoea, ulcerations, nausea, emesis and severe malabsorption followed by infections with dehydration and electrolyte disorders have to be encountered (Fig. 2).

The following section will therefore inform on the prevention and treatment of acute side effects following the treatment of gastrointestinal cancer by chemotherapy and radiation.

Management of oral and gastrointestinal mucosal injury

Oral and gastrointestinal mucositis caused by radiation with or without chemotherapy continues to represent an important clinical problem. Mucositis is defined as inflammatory and/or ulcerative lesion of a given part of the oropharyngeal, oesophageal, and other gastrointestinal mucosa that typically manifests as erythema, patchy or confluent white lesions (see Fig. 1) and may eventually become ulcerative in nature. Besides ionizing radiation numerous chemotherapeutic agents are well known to play a causal role in the development of any mucositis. Among these, fluorouracil, irinotecxan, leucovorine, vinorelbine, docetaxel, paclitaxel, oxaliplatin, carboplatin, cisplatin, and gemcitabine may represent the subgroup mostly used for chemoradiation in gastrointestinal cancer.

With an incidence of ca. 25% for diarrhoea of grade 3–4 both irinotecan and oxaliplation [7] applied with fluorouracil may pose a significant clinical problem. Consequently, only a small subgroup of these agents may be used as typical standard regimen (see Practice Points) for combined treatment of many gastrointestinal tumour types.

Practice points (standard regimens for combined radiation and chemotherapy)

- Oesophageal cancer: Fluorouracil/platinum or paclitaxel/platinum
- Rectal Cancer: Fluorouracil (/oxaliplatin)
- Anal Cancer: Fluorouracil/Mitomycin C

On the other hand it seems necessary to emphasize that the combined administration of radiation and some chemotherapeutic agents like gemcitabine as well as targeted cancer therapeutics (e.g. TKIs and mTOR inhibitors) still represents an area of clinical research (Research Agenda) and must therefore termed as experimental. The combined application of cetuximab, cisplatin, irinotecan and radiotherapy for oesophageal cancer was recently reported to result in a treatment-related mortality rate of 10% [8].

Research agenda (combined radiation and targeted therapy)

- Cetuximab
- Bevacizumab
- Erlotinib, gefitinib
- Sorafenib, sunitinib