REVIEW ARTICLE

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Management of Chemotherapy-Induced Adverse Effects in the Treatment of Colorectal Cancer

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Abstract

The anticancer agents fluorouracil, raltitrexed, irinotecan and oxaliplatin show limited efficacy in the treatment of colorectal cancer and may be associated with substantial toxicity. Therefore, the prevention and reduction of chemotherapy-induced adverse effects is of major significance, in accordance with the increasing concern for the quality of life of patients with cancer.

Therapeutic drug monitoring of fluorouracil and chronomodulation of fluorouracil and oxaliplatin, have been effective in reducing the incidence and gravity of adverse effects in several clinical trials. However, these concepts have not been implemented in clinical practice yet. At the present time, dose adaptation and sup-

portive measures are the main tools for toxicity control in the treatment of colorectal cancer. In this review, supportive measures for alleviation of the adverse effects of fluorouracil, raltitrexed, irinotecan and oxaliplatin, respectively, are described, based on study results.

The main adverse effects of these agents are myelosuppression, oral mucositis, diarrhoea, acute cholinergic syndrome, nausea and emesis, neurotoxicity, hand-foot syndrome and other cutaneous adverse effects, ocular toxicity, cardiotoxicity, small bowel toxicity, asthenia, elevated liver transaminase levels and alopecia. The incidence and gravity of these adverse effects are more or less related to the agent and administration schedule involved. The supportive measures and recommendations include the use of specific drugs, alterations of administration schedule and several nonpharmacological methods. In addition, guidelines for dosage adjustments when toxicity occurs are presented.

For optimal management of adverse effects, patients should be considered individually, while patients, nurses and physicians should cooperate to identify and treat adverse effects in an early stage of their development.

Despite improvements in diagnosis and therapy in the last decades, the cure rates for colorectal cancer are still relatively poor. The survival benefits of chemotherapy are only modest and depend on the stage of the disease as assessed using the Dukes' staging system or the tumour node metastasis (TNM) classification system. Adjuvant treatment of Dukes' C or TNM stage III resected colon cancer with fluorouracil and levamisole has been shown to increase 5-year overall survival by 33% (from 39 to 50%) compared with untreated or levamisole-treated patients.[1,2] In addition, a pooled analysis of 3 studies revealed that fluorouracil combined with folinic acid (leucovorin) increases 3-year overall survival from 64 to 76% in patients with TNM stage III colon cancer.[3] With regard to advanced colorectal cancer, a recent meta-analysis revealed that chemotherapy increases median survival only by 3.7 months compared with no treatment.[4]

These data are based on treatment with fluorouracil. This drug has been the main anticancer treatment for colorectal cancer for decades. In recent years intensive research has been performed with new cytotoxic agents, of which raltitrexed, oxaliplatin and irinotecan have been introduced to date. In the near future oral analogues of fluorouracil and inhibitors of the fluorouracil catabolising enzyme dehydropyrimidine dehydrogenase (DPD) are expected. Moreover, innovative treatment modalities such as antiangiogenic and antimetastatic agents, farnesyl transferase inhibitors, vaccine and gene therapy are in early clinical trials.[5]

To date, fluorouracil, raltitrexed, oxaliplatin and irinotecan are being used in clinical practice for the treatment of colorectal cancer. The adverse effects profiles of the new cytotoxic drugs raltitrexed, oxaliplatin and irinotecan, are claimed by the manufacturers to be more favourable than the adverse effect profile of fluorouracil (table I). However, clinical trials have revealed that the new agents are associated with serious adverse effects, that may necessitate alteration in dose or dose interval or even discontinuation of therapy (tables II and III). Therefore, along with the increasing concern for quality of life, management of chemotherapy-induced adverse effects is of major clinical importance.

In this review, supportive measures to prevent or alleviate adverse effects are considered with regard to chemotherapy for colorectal cancer. A search of the English language literature was performed using Medline and Embase from 1985 to October 2000 using the key words toxicity, colorectal and cancer.

Hepatic arterial infusion (HAI) therapy has not been included in this review, because HAI does not represent a standard treatment option for patients with hepatic metastases from colorectal cancer at

this time.[53,54] This also applies to the oral analogues of fluorouracil and inhibitors of the fluorouracil catabolising enzyme DPD, that will be introduced in the near future. In addition, radiotherapy, which is used in the treatment of rectal cancer and other types of cancer, is beyond the scope of this review, which specifically concerns the management of chemotherapeutic toxicity.

1. Adverse Effect Profiles

The incidence of the main adverse effects associated with fluorouracil, raltitrexed, oxaliplatin and irinotecan treatment of advanced colorectal cancer are presented in tables I and II. The incidence and severity of the symptoms depend strongly on the administration schedule used. This is especially true for fluorouracil. The results of several administration schedules have been published including different toxicity data. More detailed information about the association between administration schedules and adverse effect profiles is given in Jansman et al.[55]

Moreover, different combinations of the cytotoxic drugs that have been investigated, are listed in table III.

2. General Recommendations for the Management of Adverse Effects

Early detection of adverse effects allows physicians to prevent worsening of the effects by dosage adjustment. Therefore, it is important to inform patients prior to the start of chemotherapy about the possible adverse effects and to explain the relevance of reporting these symptoms if they appear.

An alternative to dosage adjustment based on the appearance of adverse effects is the use of therapeutic drug monitoring. Several studies have been performed to investigate the relationship between pharmacokinetic and toxicity parameters of the drugs discussed. They are summarised by Jansman et al.[55] The results of these studies demonstrate that pharmacokinetics can be predictive for toxicity. For fluorouracil, some studies have even revealed that individual dosage adjustment based on pharmacokinetic parameters can reduce toxicity.[56-58] These results indicate that therapeutic drug monitoring can be beneficial in controlling adverse effects and should encourage the extension of clinical studies to dosage individualisation.

Another means of decreasing toxicity is chronomodulation of chemotherapy. Adapting continuous infusion rates to plasma concentrations of oxaliplatin and fluorouracil, has been shown to limit adverse effects and may therefore permit dosage escalation.[59-61] However, chronomodulated regimens raise a lot of practical and economic problems, that have prevented implementation in clinical practice thus far.

Therefore, to date, dosage adaptation and the application of supportive measures are the main tools for the management of chemotherapy-induced adverse effects.

3. Management of Adverse Effects in the Treatment of Colorectal Cancer

In sections 3.1 to 3.10 the management of the various adverse effects of fluorouracil, raltitrexed, oxaliplatin and irinotecan are discussed. In table IV recommendations are presented based on data currently available from the literature. Manufacturer's guidelines for dosage adjustment when toxicity occurs are also included.

The role of the new chemoprotectants, i.e. amifostine, dexrazoxane, glutathione, mesna, and ORG 2766, in the prevention or the relief of chemotherapy-induced adverse effects has been investigated in the treatment of various types of cancer.[67,68] Since there are no published data available yet with regard to the effect of chemoprotectants in the treatment of colorectal cancer, they will not be considered further.

3.1 Myelosuppression

Myelosuppression is an adverse effect of all the cytostatic agents discussed in this review. Management of chemotherapy-associated neutropenic fever or infection has customarily involved treatment with intravenous antibacterials, usually accompanied by hospitalisation. The haematopoietic colony-stimulating factors (CSFs) have been introduced

table I

into clinical practice as additional supportive measures that can reduce the likelihood of neutropenic complications caused by chemotherapy.[69]

The guidelines of the American Society of Clinical Oncology, updated in 1996, 1997 and 2000, however, do not recommend intervention with a CSF in patients with afebrile neutropenia, because clinical data do not show clinical benefit for the routine use of CSFs in afebrile patients at the time that neutropenia is diagnosed.[70-72] Yet certain patients with fever and neutropenia are at higher risk of infection-associated complications and have prognostic factors that are predictive of poor clinical outcome. Therefore, the guidelines of the society also indicate that the use of CSF together with antibiotics may be considered for febrile neutropenic patients with risk factors for clinical deterioration. These factors include profound neutropenia (absolute neutrophil count < 100/μl), uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome) and invasive fungal infection.[70-72]

3.2 Oral Mucositis

Managing fluorouracil-induced oral mucositis, as one of the major dose-limiting toxicities, has been the subject of many studies. For assessing the efficacy of treatment or prophylaxis the lack of an accepted, validated scoring system for mucositis has always been an impediment. Recently, a scoring system has been published that may permit objective comparisons of different protective agents in future.[73] The currently available, sometimes inconsistent, study results indicate that for prevention of oral mucositis, a mouthwash or rinse with benzydamine, chlorhexidine, sucralphate, saline, bicarbonate or just sterile water may be beneficial, as well as administration of betacarotene, dinoprostone (prostaglandin E2), granulocyte CSF, pentoxifylline, silver nitrate, or a combination of polymyxin B, tobramycin and amphotericin B.[74-76] For treatment of established mucositis, a sucralfate oral suspension, capsaicin, lidocaine (lignocaine) or tocopherol (vitamin E) may be considered.[74] However, the majority of trials with these prophylactic

Table I. Adverse effect data for fluoruoracil (FU)-folinic acid (FA) therapy in advanced colorectal cancer[a]

Dose (mg/m^2)	Frequency of administration	No. of patients (cumulative)	Patients with >grade 2 toxicity (%)[b]							% TRD	Reference
			leucopenia	thrombo-cytopenia	mucositis	diarrhoea	nausea	vomiting	hand-foot syndrome		
FU 370-400 bolus/FA 200 bolus	D × 5, every 3-5W	403	4-19	5	14-30	9-19	3-8	6	NR	0-2	6-10
FU 370-425 bolus/FA 20 bolus (Mayo regimen)	D × 5, every 3-5W	742	17-29	0-3	12-28	7-18	3-10	5-9	NR	0-3	6,7,10-14
FU 500-600 bolus/FA 500 bolus/2-3h infusion (Roswell Park regimen)	D1, every W × 6, 2W rest	626	0-10	0-3	0-10	20-40	4-10	5	NR	0-6	12,13,15-18
FU 500-600 bolus/FA 20-25 bolus/2h infusion	D1, every W × 6, 2W rest	255	1-4	1	0	13-16	6	NR	NR	0-4	17,18
FU 300-500 bolus + 400-600 22h infusion/FA 200 2h infusion (De Gramont regimen)	D1, D2 every 2W	309	2-3	NR	0-2	0-16	0-14	0	0	0	9,19,20
FU 2600 24h infusion/FA 100-500 2-24 h infusion (AIO regimen)	D1, every W	271	0-1	0	0-14	0-29	0-14	0-5	3-19	0-5	21-26
FU 200 continuous infusion/FA 20 bolus	D1-D28, 1W rest/D1, D8, D15, D22, every 5W	122	0	0	11	11	NR	5	24[c]	0	12,27

a The data summarised includes those administration schedules that have been studied separately at least twice and results that have been published as full papers in the period from 1985 until October 2000.

b Minimum and maximum percentages as found in references.

c Any grade.

AIO = Arbeitsgemeinschaft für Internistische Onkologie (Association of Medical Oncology of the German Cancer Society); **D** = day; **NR** = not reported; **TRD** = toxicity/treatment-related deaths; **W** = week(ly).

Table II

and therapeutic agents were not placebo-controlled, with the exception of those with benzydamine, chlorhexidine and sucralfate.[74-76]

Furthermore, nonpharmacological methods such as routine mouth care, an adequate diet and helium-neon laser treatment have proven to be efficacious, although the results are preliminary, the number of patients treated small and/or trials were uncontrolled.[74,75,77,78] Only preventive oral cooling (cryotherapy) with ice chips has been demonstrated to decrease fluorouracil-induced oral mucositis in 2 controlled trials involving 95 and 84 patients, respectively.[79,80]

However, at the present time, no prophylaxis or treatment has been shown to be uniformly efficacious and can be accepted as evidence based standard therapy. Until the preferred agent or method has been assessed in comparative trials, oral cooling seems favourable for patients, who are at risk of developing chemotherapy-induced oral mucositis, because it is simple, inexpensive and well tolerated. Oral cryotherapy should be applied for 30 minutes given at around the same time as the fluorouracil therapy.[77,79,80] When fluorouracil is combined with oxaliplatin, oral cryotherapy is contraindicated because of a possible provocation of laryngo-pharyngal dysesthesia by oxaliplatin (see section 3.6).

3.3 Diarrhoea

Diarrhoea is a dose-limiting adverse effect of fluorouracil, raltitrexed and irinotecan. The pathophysiological mechanism responsible for the severity of irinotecan-induced diarrhoea differs from that of fluorouracil- and raltitrexed-induced diarrhoea.[81,82]

Two types of diarrhoea have been reported as an adverse effect of irinotecan treatment, i.e. early diarrhoea and delayed diarrhoea. The early diarrhoea, occurring during or immediately after irinotecan infusion, is assumed to be the result of increased cholinergic activity.[83] This type of diarrhoea is mostly accompanied with other cholinergic symptoms (see section 3.4) and is readily control-

Table II. Adverse effect data for single-agent therapy with raltitrexed, irinotecan or oxaliplatin in advanced colorectal cancer

Agent/dose (mg/m^2)	Frequency of administration	No. of patients (cumulative)	Patients with >grade 2 toxicity (%)[a]							% TRD	Reference
			leucopenia	neutropenia	thrombo-cytopenia	mucositis	diarrhoea	nausea/ vomiting	neurosensory/ peripheral neuropathy		
Raltitrexed 3 15min infusion	D1, every 3W	646	6-15	NR	1-4	0-2	10-14	9-13	NR	2-4	28-30
Irinotecan 100-125 90min infusion	D1, every W × 4, 2W rest	166	NR	20	1	NR	27[b]	10	NR	0	31
Irinotecan 125-150 90min infusion	D1, every W × 4, 2W rest	48	25	31	2	NR	37[b]	10	NR	0	32
Irinotecan 300-350 30-90min infusion	D1, every 3W	796	35	14-46	1-2	0-2	10-38[b]	11-20	NR	0-2	33-37[c]
Irinotecan 175 90min infusion	D1, D10/D11, every 3W	30	NR	12	NR	NR	4[b]	5	NR	NR	37[c]
Oxaliplatin 130 2h infusion	D1, every 3W	169	NR	0-5	0-8	3	0-10	8-17	0-31	0	38-40

a Minimum and maximum percentage, found in references.

b Late diarrhoea.

c Preliminary results.

D = day; **NR** = not reported; **TRD** = toxicity/treatment-related deaths; **W** = week(ly).

Table III

led by an anticholinergic agent, e.g. subcutaneous atropine sulfate 0.25mg.[34]

The irinotecan-induced delayed diarrhoea, defined as diarrhoea occurring more than 24 hours after drug infusion, is suggested to be caused by the active metabolite SN-38 formed by deconjugation of the SN-38 glucuronide by intestinal bacteria.[82,84] This type of diarrhoea usually develops in the first week after administration with the weekly schedule and in the second or third week with the 3-weekly schedule, respectively, probably because of a secretory mechanism with an exudative component.[84] Patients are advised to drink large volumes of electrolyte solutions after the first liquid stool has emerged. The effect of anticholinergic drugs on this type of diarrhoea is limited, but high dose loperamide initiated at first signs of diarrhoea has been proven to control irinotecan-induced diarrhoea effectively and allowed the administration of high doses of irinotecan.[32,85,86] Also, a combination of loperamide and acetorphan, an antidiarrhoeal that acts purely as an antisecretory intestinal drug, has been found to be effective in controlling the diarrhoeal episodes. Further studies have been recommended to determine the optimal treatment of delayed diarrhoea based on the proposed underlying secretory mechanism.[84]

Another mechanism that might be involved in chemotherapy-induced diarrhoea is glutamine depletion, which develops in patients with cancer over time. At this time, a prospective study is underway to confirm the preliminary positive results with oral glutamine suppletion in preventing late onset irinotecan-related diarrhoea.[87]

Irinotecan- and fluorouracil-induced World Health Organization (WHO) grade 3 to 4 diarrhoea that is refractory to loperamide may be eligible for treatment with oral budesonide 9mg given once daily for 3 to 5 days. In a phase I trial, budesonide treatment of loperamide-resistant severe diarrhoea resulted in a reduction of stool frequency by at least 2 grades according to the National Cancer Institute/WHO classification in 12 of 14 patients (86%) treated with irinotecan and in 4 of 7 patients (57%) treated with fluorouracil.[88]

Table III. Adverse effect data for combination chemotherapy used in advanced colorectal cancer

Agent/dose (mg/m^2)	Frequency of administration	No. of patients (cumulative)	Patients with >grade 2 toxicity (%)[a]							% TRD	Reference
			neutropenia	thrombo-cytopenia	mucositis	diarrhoea	nausea/ vomiting	hand-foot syndrome	neurosensory/ peripheral neuropathy		
Irinotecan 80-350 90min infusion/FU bolus and/or continuous infusion/FA low dose or high dose	Variable	490	15-64	0	0-9	12-24	9-15	<1	NR	0-1	41-44
Oxaliplatin 50-135 2-6h infusion/FU bolus and/or continuous infusion/FA	Variable	651	10-42	2-13	0-18	0-53	0-28	0-3	0-28	0-2	45-51
Irinotecan 80 30min infusion Oxaliplatin 85 2h infusion	D1, D8, D15, every 4W D1, D15, every 4W	36	19	6	0	19	17	NR	8	0	52

a Minimum and maximum percentage found in references.

D = day; **FA** = folinic acid; **FU** = fluorouracil; **NR** = not reported; **TRD** = toxicity/treatment-related deaths; **W** = week(ly).

Table IV. Management of the adverse effects of anticancer agents used in colorectal cancer

Agent	Adverse effect	Support measures	Specific recommendations
Fluorouracil[a]	Myelosuppression		Haematopoietic CSF + antibacterials in febrile patients with neutropenia with risk factors for clinical deterioration If moderate haematological toxicity: 20% dose reduction[b] If severe haematological toxicity: 30% dose reduction[b] If leucocyte count <3500/mm^3 or platelet count <100 000/mm^3: discontinuation[b] Switch to weekly administration schedule or continuous infusion[a]
	Oral mucositis	Oral cooling/ice chips for 30 minutes at around start of bolus fluorouracil	If moderate gastrointestinal toxicity: 20% dose reduction[b] If severe gastrointestinal toxicity: 30% dose reduction[b] Switch to weekly administration schedule[a]
	Diarrhoea	Loperamide 2mg every 2 hours starting at initial signs of diarrhoea	SC octreotide 100 to 150μg 3 times daily for severe diarrhoea and diarrhoea refractory to loperamide PO budesonide 9 mg/day for 3 to 5 days for NCI/WHO grade 3 to 4 diarrhoea refractory to loperamide If moderate gastrointestinal toxicity: 20% dose reduction[b] If severe gastrointestinal toxicity: 30% dose reduction[b] Switch to Mayo regimen[a]
		Oral or intravenous rehydration Electrolyte replacement Broad spectrum antibacterials	If diarrhoea persists over 24 hours
	Nausea/emesis	Metoclopramide	If moderate gastrointestinal toxicity: 20% dose reduction[b] If severe gastrointestinal toxicity: 30% dose reduction[b] For prevention at 30 min before start of chemotherapy: dexamethasone, prochlorperazine, thiethylperazine or metoclopramide in combination with diphenhydramine with or without lorazepam
	Hand-foot syndrome	Pyridoxine (vitamin B6) 50 to 150 mg/day	Switch to bolus injection[a]
	Erythema or increased cutaneous pigmentation		Avoid strong sunlight
	Ocular toxicity	Ice packs for 30 minutes starting 5 minutes prior to chemotherapy	
	Cardiotoxicity Small bowel toxicity Alopecia		Withdrawal of fluorouracil/fluorouracil replacement Continuation with a lower dose after acute toxicity period Wig or toupee
Raltitrexed	Myelosuppression		Haematopoietic CSF + antibacterials in febrile patients with neutropenia with risk factors for clinical deterioration If WHO grade 3 haematological toxicity: 25% dose reduction[c] If WHO grade 4 haematological toxicity: 50% dose reduction[c] If WHO grade 4 haematological toxicity + WHO grade 3 gastrointestinal toxicity: discontinuation[c]

Continued on next page

Table IV. Contd

Agent	Adverse effect	Support measures	Specific recommendations
	Oral mucositis	Oral cooling/ice chips for 30 minutes at around start of chemotherapy	If WHO grade 2 mucositis: 25% dose reduction[c] If WHO grade 3 mucositis: 50% dose reduction[c] If WHO grade 4 mucositis or WHO grade 3 mucositis + WHO grade 4 haematological toxicity: discontinuation[c]
	Diarrhoea	Loperamide 2mg every 2 hours starting at initial signs of diarrhoea	SC octreotide 100 to 150μg 3 times daily for severe diarrhoea and diarrhoea refractory to loperamide If WHO grade 2 diarrhoea: 25% dose reduction[c] If WHO grade 3 diarrhoea: 50% dose reduction[c] If WHO grade 4 diarrhoea or WHO grade 3 diarrhoea + WHO grade 4 haematological toxicity: discontinuation[c]
		Oral or intravenous rehydration Electrolyte replacement Broad spectrum antibacterials	If diarrhoea persists over 24 hours
	Nausea/emesis	Metoclopramide	
Irinotecan	Myelosuppression		Haematopoietic CSF + antibacterials in febrile patients with neutropenia with risk factors for clinical deterioration If WHO grade 4 neutropenia or WHO grade 3 to 4 with WHO grade 2 to 4 fever or WHO grade 4 thrombocytopenia or WHO grade 4 leucopenia: 15 to 20% dose reduction (and/or fluorouracil dosage reduction when combined)[c]
	Acute diarrhoea/cholinergic syndrome	SC atropine sulfate 0.25mg	Prolongation of infusion duration to at least 90 minutes
	Delayed diarrhoea	Loperamide 2mg every 2 hours starting at initial signs of diarrhoea	SC octreotide 100 to 150μg 3 times daily for severe diarrhoea and diarrhoea refractory to loperamide PO budesonide 9 mg/day for 3 to 5 days for NCI/WHO grade 3 to 4 diarrhoea refractory to loperamide If WHO grade 3 to 4 diarrhoea: postpone administration of next course until full recovery of symptoms and reduce dose (and/or fluorouracil dose when combined) with 15 to 20%[c]
		Oral or intravenous rehydration Electrolyte replacement, Broad spectrum antibacterials	If diarrhoea persists over 24 hours
	Nausea/emesis	Serotonin 5-HT_3 antagonist	Also for prevention before start of chemotherapy: 5-HT_3 antagonist in combination with dexamethasone with or without lorazepam If WHO grade 3 to 4 nausea/emesis: postpone administration of next course until full recovery of symptoms and reduce dose (and/or fluorouracil dose when combined) with 15 to 20%[c]
Oxaliplatin	Myelosuppression		Haematopoietic CSF + antibacterials in febrile, neutropenic patients with risk factors for clinical deterioration If neutrophils $<1.5 \times 10^9$/L or platelets $<50 \times 10^9$/L postpone administration of next course until values have been normalised[c] Oxaliplatin combined with fluorouracil: if neutrophils $<1.0 \times 10^9$/L or platelets $<50 \times 10^9$/L: 25% dose reduction of oxaliplatin[c]

Table IV cont.

Late diarrhoea caused by irinotecan, as well as fluorouracil-and raltitrexed-induced diarrhoea, is sometimes accompanied by severe neutropenia. Because patients with diarrhoea and neutropenia are at increased risk of developing severe infectious complications, prophylactic treatment with a broad spectrum antibacterial is indicated if diarrhoea persists for more than 24 hours.[36]

In 1998 the consensus of an expert multidisciplinary panel was published.[82] This panel was convened to formulate clinical practice guidelines for the treatment of chemotherapy-induced diarrhoea. The panel consensus was that loperamide 2mg every 2 hours is the treatment of choice for short term management of diarrhoea. This recommendation is similar to the current treatment guideline for irinotecan-induced (delayed) diarrhoea as originally described by Abigerges et al.[86] Furthermore, the panel stated, that subcutaneous octreotide 100 to 150μg 3 times daily should be considered for patients who have severe diarrhoea and in whom the diarrhoea is refractory to loperamide therapy. Octreotide directly acts on epithelial cells to reduce the secretion of a number of pancreatic and gastrointestinal hormones and has been shown to prolong intestinal transit time, promote intestinal absorption of electrolytes, decrease mesenteric blood flow and decrease secretion of fluids and electrolytes.[82] It must be emphasised, however, that no clear understanding of the optimal dosage currently exists. As for mucositis, the panel suggested that validated measures of diarrhoea have to be developed and studied in clinical trials as part of standard evaluation and care.[82]

3.4 Acute Cholinergic Syndrome

Irinotecan treatment is often accompanied by acute cholinergic adverse effects (see section 3.3) such as abdominal cramps, diarrhoea, diaphoresis, hypotension, bradycardia, rhinitis, salivation, visual disturbances and lacrimation. This cholinergic syndrome has been attributed to the piperidine structure of the irinotecan molecule, which mimics a cholinergic drug when dissociated by esterases to form SN-38.[83] The adverse effects can be treated

	Diarrhoea	Loperamide 2mg every 2 hours starting at initial signs of diarrhoea	SC octreotide 100 to 150μg 3 times daily for severe diarrhoea and diarrhoea refractory to loperamide Oxaliplatin combined with fluorouracil: if WHO grade 4 diarrhoea: 25% dose reduction of oxaliplatin[c]
		Oral or intravenous rehydration Electrolyte replacement	
		Broad spectrum antibacterials	If diarrhoea persists over 24 hours
	Nausea/emesis	5-HT_3 antagonist	Also for prevention before start of chemotherapy with infusion durations of 6 hours or less Avoid cold food or drink and contact with cold surfaces during and shortly after infusion
	Neurotoxicity		If neurological symptoms persist over 7 days or if paraesthesia without functional impairment persist until next cycle: dose reduction from 85 to 65 mg/m^2, if paraesthesia with functional impairment persist until next cycle: discontinuation[c]

a Toxicity profile is largely dependent on administration schedule: leucopenia and mucositis more frequent and diarrhoea less frequent with Mayo regimen than with weekly administration,[16] haematological toxicity more frequent and hand-foot syndrome less frequent with bolus injection than with continuous infusion.[62]

b Data from AHFS Drug Information 2000.[63]

c Recommendation by manufacturer.[64-66]

CSF = colony-stimulating factor; **NCI** = National Cancer Institute; **PO** = oral; **SC** = subcutaneous; **WHO** = World Health Organization; **5-HT**= seratonin (5-hydroxytryptamine).

effectively with subcutaneous atropine sulfate 0.25mg. Also, prolongation of the infusion duration to at least 90 minutes can prevent or reduce the cholinergic toxicity.[34]

3.5 Nausea and Emesis

For the prevention and treatment of acute and delayed emesis by chemotherapy alizapride, prochlorperazine, thiethylperazine, metoclopramide, lorazepam, serotonin 5-HT_3 antagonists and dexamethasone are used. For moderate to high emetogenic anticancer agents numerous studies have been carried out to determine the most appropriate scheme and schedule of antiemetic treatment. However, for low to moderate emetogenic agents, including the drugs discussed in this review, the optimal antiemetic treatment has not been established.[89]

Hesketh et al.[90,91] have described a system for classifying the acute emetogenity of chemotherapy into 5 levels, based on the percentage of patients experiencing emesis within 24 hours after chemotherapy without antiemetic prophylaxis. According to this classification system, fluorouracil at doses less than 1000 mg/m^2 is considered a level 2 agent and irinotecan a level 3 agent, causing vomiting in 10 to 30% and 30 to 60% of patients, respectively. To date, raltitrexed and oxaliplatin have not yet been classified. For antiemetic prophylaxis, the National Comprehensive Cancer Network has developed guidelines, that have been applied to the classification system.[92] For chemotherapy with level 2 acute emetogenic potential (fluorouracil), antiemetic prophylaxis with dexamethasone, prochlorperazine, thiethylperazine or metoclopramide in combination with diphenhydramine with or without lorazepam is recommended. For level 3 agents (irinotecan), 5-HT_3 antagonists in combination with dexamethasone with or without lorazepam are advised.[90-92]

In the studies that have been performed with irinotecan or oxaliplatin, monotherapy with metoclopramide or alizapride, metoclopramide combined with dexamethasone or 5-HT_3 antagonists have been used for managing nausea and emesis.[72,93,94] For prevention of these adverse effects, the manufacturers of both irinotecan and oxaliplatin recommend the use of 5-HT_3 antagonists.[64,65] For oxaliplatin, this recommendation especially applies to infusion durations of 6 hours or less.[38,39,95] For fluorouracil and raltitrexed, no specific antiemetic treatment has been used in clinical trials, nor have specific recommendations been made by the manufacturers. Since fluorouracil has been classified as a level 2 agent, metoclopramide may be the appropriate choice for prevention and treatment of nausea and emesis induced by this agent. This may also apply to raltitrexed, since there are no data available involving the use of alternative antiemetic drugs such as 5-HT_3 antagonists.

3.6 Neurotoxicity

The dose-limiting sensory neuropathy of oxaliplatin is characterised by paraesthesia and dysesthesia in hands, feet and the peri-oral area. It has often been observed during oxaliplatin infusion, lasted for a few minutes to a few days or even months, and appeared to be reversible. The acute symptoms develop within hours, either during or after infusion in 80 to 85% of patients. Some patients reported laryngo-pharyngal dysesthesia when swallowing cold food or drink or touching cold surfaces. Therefore, the intake of cold food or drink during or shortly after infusion and contact with cold surfaces should be avoided.[38,39,96] In addition, recurrence of laryngo-pharyngal dysesthesia can be prevented effectively by prolonging the infusion duration to 6 hours.[40,94]

Because the neurological scales available were not sufficient for grading the characteristics of the neurotoxicity associated with oxaliplatin use, a specific grading system has been developed that takes into account both the intensity and duration of toxicity-related symptoms.[61] A safety evaluation in 682 patients from 9 studies revealed that at a mean cumulative dose of 900 mg/m^2 of oxaliplatin, 12% of patients experienced grade 3 neurotoxicity (functional impairment) according to the specific grading system. The Kaplan-Meier model demonstrated, that the risk of developing severe

neurotoxicity was 10% after 6 cycles (780 mg/m^2) and 50% after 9 cycles (1170 mg/m^2). After discontinuation in patients with grade 2 or more neuropathy, regression of symptoms was observed in 82% of these patients and disappearance in 41%.[97]

3.7 Hand-Foot Syndrome and Other Cutaneous Adverse Effects

Hand-foot syndrome, also known as chemotherapy-induced acral erythema or palmoplantar erythrodysesthesia, is a localised cuteneous reaction to certain systemic anticancer drugs. Fluorouracil is among the drugs mostly involved in this self-limiting reaction. Pyridoxine at oral dosages ranging from 50 to 150 mg/day has been reported to be successful in managing the symptoms in some case reports or studies with small numbers of patients.[98-101] Therefore, pyridoxine may be considered in case of palmoplantar erythrodysesthesia development, although confirmatory evidence in placebo-controlled randomised trials is needed.

Other dermatological manifestations of fluorouracil toxicity include dry skin and fissuring, diffuse erythema, scaling, and photosensitivity manifested by erythema or increased pigmentation. Exposure to strong sunlight may intensify these skin reactions.[63]

For raltitrexed, cutaneous toxicity has been reported in 13% of patients.[64]

3.8 Ocular Toxicity

Fluorouracil, either alone or as part of a combination chemotherapy regimen, causes ocular toxicity in 25 to 38% of patients.[102] The ocular adverse effects consist of blurred vision, ocular pain, photophobia, excessive lacrimation, eye irritation, conjunctivitis, circumorbital oedema, and keratitis. These symptoms are usually mild to moderate, although in some cases discontinuation of chemotherapy is necessary because of marked ocular discomfort. After cessation of treatment the symptoms generally resolve within 1 to 2 weeks.[102]

A North Central Cancer Treatment Group (NCCTG) clinical trial has been performed to test the effect of ocular ice packs on fluorouracil-induced ocular toxicity in 62 patients, similar to oral cryotherapy in the treatment of oral mucositis.[103] The ice packs were applied for 30 minutes, starting 5 minutes prior to intravenous injection of fluorouracil. Crossover analyses demonstrated decreased ocular toxicity with ocular ice pack therapy ($p = 0.001$). The therapy was well tolerated by most of the study participants.[103] However, whether ice packs are also effective in the treatment of ocular toxicity, that has already developed, is yet unknown. In clinical practice, administration of methylcellulose or dexamethasone eyedrops can ameliorate symptoms.

3.9 Cardiotoxicity

Fluorouracil has been reported to be cardiotoxic with an estimated incidence varying widely from 1.2 to 18% of patients.[104] Fluorouracil cardiotoxicity is more common after high dose continuous infusion therapy than after bolus doses.[105] The main symptoms are angina-like chest pain, cardiac arrhythmias or myocardial infarction. With the exception of myocardial infarction, these symptoms are usually reversible after discontinuation of fluorouracil administration. A prospective cohort study following 1 cycle of fluorouracil infusion in 483 patients revealed that pre-existing cardiac disease [relative risk (RR) = 6.83; $p = 0.002$], use of calcium antagonists (RR = 4.75; $p = 0.014$) and use of nitrates (RR = 9.18; $p = 0.007$) were risk factors for cardiotoxicity.[104]

Since no effective prophylaxis or treatment has yet been proven to be efficacious in cardiotoxicity, fluorouracil should be withdrawn and replaced by another chemotherapeutic regimen.[106] If further treatment with fluorouracil is warranted, it should be administered in a cardiac unit with careful monitoring.[107]

3.10 Small Bowel Toxicity

Recently, Fata et al.[108] described 6 case reports of patients who had developed acute small bowel toxicity with clinical signs of acute abdominal pain and diarrhoea after treatment with fluorouracil and folinic acid. As with cardiotoxicity, it is difficult to

predict which patients may be at risk for developing small bowel toxicity. However, although the symptoms may recur after rechallenge, cautious continuation with a lower dose of fluorouracil can be considered after the acute toxicity period.[108]

3.11 Other Adverse Effects

Asthenia frequently occurs in patients treated with fluorouracil (2%),[32,33,109] raltitrexed (5 to 12%)[55] and irinotecan (6 to 24%).[55] This adverse effect is usually reversible, and can be accompanied by malaise and a flu-like syndrome.[29,30,32,34,36,72,85,93,109,110]

Furthermore, reversible elevations of liver transaminase levels (AST and ALT) have been reported regularly in clinical trials with raltitrexed (10 to 13% of patients)[55] and irinotecan (9% of patients).[65] These elevations were mostly asymptomatic and self-limiting, and are unlikely to be clinically significant.[29,30,34,85,109,111]

Alopecia is a common adverse effect of irinotecan therapy (11 to 59% of patients)[55] and fluorouracil therapy (0 to 40% of patients)[11,34,36,55,72,85,93,110] Although harmless and reversible, patients should be offered a cosmetic makeshift (wig, toupee, etc.) because of the negative social impact of alopecia. For the prevention of chemotherapy-induced alopecia, scalp cooling has been proven to be efficacious when different combinations of taxanes, anthracyclines and etoposide have been used.[112] Therefore, additional clinical trials seem warranted to test the preventive effect of scalp cooling on fluorouracil– and irinotecan-induced alopecia.

4. Conclusion

Despite the supposed safety of the new chemotherapeutic agents for treatment of colorectal cancer, their toxicity should not be underestimated. In order to reduce toxicity, identification and management of adverse effects at their first appearance are needed, especially with the introduction of several combinations of fluorouracil, raltitrexed, irinotecan and oxaliplatin, in numerous administration schedules, leading to different adverse effect profiles.[52,113] Therefore, toxicity management should be individualised to the anticancer agent or agents, administration schedule and patient. In addition, patients, nurses and physicians should cooperate in the detection and management of adverse effects at an early stage.

Therapeutic drug monitoring of fluorouracil and chronomodulation of fluorouracil and oxaliplatin have been shown to limit toxicity in clinical trials. However, these concepts are not implemented in clinical practice yet. To date, dosage adjustment and intensive supportive measures are the main tools for managing chemotherapy-induced adverse effects.

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