REVIEW ARTICLE

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Risk Factors Determining Chemotherapeutic Toxicity in Patients with Advanced Colorectal Cancer

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Abstract

Antitumour therapy in advanced colorectal cancer has limited efficacy. For decades, fluorouracil has been the main anticancer drug for the treatment of colorectal cancer. Recently, however, new agents have been introduced: raltitrexed, irinotecan and oxaliplatin.

Currently, the dosage for an individual patient is calculated from the estimated body surface area of the patient. Toxicity, however, frequently necessitates decreasing the dosage, extending the dose interval or even discontinuing treatment. Risk

factors with predictive value for toxicity have been identified in several studies. These risk factors are often determined by the pharmacokinetic and pharmacodynamic properties of the drug. In this review, the risk factors for toxicity of the cytotoxic agents used in the treatment of advanced colorectal cancer are considered. For fluorouracil, age, gender, performance status, genetic polymorphism of dihydropyridine dehydrogenase, drug administration schedule, circadian rhythm of plasma concentrations, history of previous chemotherapy-related diarrhoea, xerostomia, low neutrophil levels, and drug-drug interactions have been identified as affecting chemotherapeutic toxicity. For raltitrexed, gender and renal and hepatic impairment, and for oxaliplatin, renal impairment and circadian rhythm of plasma concentrations, respectively, can be considered as risk factors for toxicity. In addition, age, performance status, bilirubinaemia, genetic polymorphism of uridine 5′-diphosphate-glucuronyltransferase-1A1 and drug administration schedule have been shown to be related to irinotecan toxicity.

The available literature suggests that dose adjustment based on these risk factors can be used to individualise the dose in order to decrease toxicity and to improve the therapeutic index. This also applies to therapeutic drug monitoring, which has been shown to be effective controlling the toxicity of fluorouracil in some studies.

Future research is warranted to assess the potential advantage of dose individualisation of chemotherapy founded on risk factors, over direct dose calculation from the estimated body surface area, with regard to toxicity, therapeutic index, and quality of life, in patients with advanced colorectal cancer.

Colorectal cancer is second to lung cancer in men and to breast cancer in women as the most common cause of death from cancer in the industrialised countries.[1] In Europe and the US, about 300 000 new cases of colorectal cancer are diagnosed and 200 000 deaths are registered each year.[2] With over half of all diagnosed patients dying as a result of metastatic spread, the prognosis of colorectal cancer is poor.[3]

Prognosis and survival are largely dependent on early detection and directly related to the pathophysiological tumour stage at the time of diagnosis. To define the tumour stage, the tumour node metastasis classification or the modified Dukes' staging system (grades A to D) are used. The staging systems use the extent of cancer penetration through the bowel wall, the number of lymph nodes involved and the presence of distant metastases to grade cancer severity.[4,5]

The first-line treatment for patients with colorectal cancer is radical surgery of the primary tumour. Adjuvant therapy currently consists of chemotherapy and, for rectal cancer, radiotherapy. Adjuvant immunotherapy, gene therapy and treatment with biological agents are currently under clinical investigation.[2] For palliative treatment of advanced disease, surgery, chemotherapy and radiotherapy can be considered in order to improve the patient's duration and quality of life.[6]

For many years, chemotherapy has been limited to treatment with regimens containing fluorouracil. With adjuvant treatment with fluorouracil–based chemotherapy for Dukes' C colon cancer, an absolute survival improvement of 5% is achieved compared with controls, while in advanced colorectal cancer fluorouracil–based chemotherapy increases survival by 6 to 12 months.[2] In recent years, intensive research into new cytotoxic agents has been performed, of which raltitrexed, oxaliplatin and irinotecan seem the most promising.

Although fluorouracil-based chemotherapy has been used for 40 years, patients taking this agent can still experience substantial toxicity. In table I, the toxicity data of different schedules of fluorouracil in combination with folinic acid (leucovorin) are presented.[7-28] The efficacies of the different schedules are more or less the same, although continuous infusion may be more efficacious than bolus injection.[7,29] The available toxicity data for raltitrexed,

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Table I. Toxicity 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	Ref
			leucopenia	thromboytopenia	mucositis	diarrhoea	nausea	vomiting	alopecia[c]	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	11-40	NR	0-2	8-12
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	2-34	NR	0-3	7-9, 12-15
FU 500-600 bolus/FA 500 bolus/2-3h infusion (Roswell Park regimen)	D1, every W times 6, 2W rest	626	0-10	0-3	0-10	20-40	4-10	5	4	NR	0-6	13,14, 16-19
FU 500-600 bolus/FA 20-25 bolus/2h infusion	D1, every W times 6, 2W rest	255	1-4	1	0	13-16	6	NR	NR	NR	0-4	18,19
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	1-3	0	0	7,20, 21
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	0-18	3-19	0-5	22-27
FU 200 continuous infusion/FA 20 bolus	D1-D28, 1W rest/D1, D8, D15, D22, every 5W	122	0	0	11	11	NR	5	NR	24[c]	0	13,28

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 March 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; **H** = hour(ly); **NR** = not reported; **TRD** = toxicity/treatment related deaths; **W** = week(ly).

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Table II. Toxicity 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	Ref
			leucopenia	neutropenia	thrombocytopenia	anaemia	mucositis	diarrhoea	nausea/vomiting	asthenia	alopecia[b]	neurosensory/peripheral neuropathy	pain	elevated transaminase levels		
Raltitrexed 3 15min infusion	D1, every 3W	646	6-15	NR	1-4	5-9	0-2	10-14	9-13	5-12[c]	NR	NR	5	10-13	2-4	30-32
Irinotecan 100-125 90min infusion	D1, every W times 4, 2W rest	166	NR	20	1	5	NR	27[d]	10	16	25 (grade 2)	NR	NR	NR	0	33
Irinotecan 125-150 90min infusion	D1, every W times 4, 2W rest	48	25	31	2	10	NR	37[d]	10	6	NR	NR	2 (abdominal)	NR	0	34
Irinotecan 300-350 30-90min infusion	D1, every 3W	796	35	14-46	1-2	7-11	0-2	10-38[d]	11-20	8-18	11-59	NR	17-33	NR	0-2	35-38, 39[e]
Irinotecan 175 90min infusion	D1, D10/D11, every 3W	30	NR	12	NR	NR	NR	4[d]	5	24	34 (> grade 3)	NR	NR	NR	NR	39[e]
Oxaliplatin 130 2h infusion	D1, every 3W	169	NR	0-5	0-8	0-5	3	0-10	8-17	NR	NR	0-31	NR	NR	0	40-42

a Minimum and maximum percentage, found in references.

b Any grade.

c Severe, not WHO/National Cancer Institute common toxicity criteria graded.

d Late diarrhoea.

e Preliminary results.

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

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irinotecan and oxaliplatin are shown in table II[30-42] and the toxicity data from phase II/III studies with different combinations of irinotecan, oxaliplatin and fluorouracil-folinic acid are shown in table III.[43-53] Currently, the dosage of chemotherapy for an individual patient is calculated from the estimated body surface area of the patient. However, toxicity frequently necessitates decreasing the dosage, extending the dose interval or even discontinuing treatment. Risk factors with predictive value for toxicity have been identified in several studies and are discussed in this review. These risk factors are often determined by the pharmacokinetic and pharmacodynamic properties of the drug. Based on the risk factors, the most appropriate dose, dose schedule and/or supportive measures may be determined for the individual patient in order to reduce toxicity and thereby improve the therapeutic index.

In addition, the results of studies looking at the use of therapeutic drug monitoring in the treatment of colorectal cancer are discussed as well as the significance of this approach for controlling toxicity.

Relevant articles for inclusion in this review were identified by performing a literature search of English language articles published from 1980 to March 2000 using MEDLINE and Embase with the keywords pharmacokinetics, colorectal, cancer, toxicity and dose.

Table III

1. Risk Factors for Toxicity

Several risk factors for toxicity have been described in the literature for fluorouracil, raltitrexed, irinotecan and oxaliplatin (table IV).[14,29,31-33,39,54-77] Sometimes they were described as dependent or independent risk factors, but mostly this was not specified. Also, determination of the predictive value of risk factors for toxicity was, frequently, not the primary goal of the study but was considered secondary to overall efficacy and toxicity assessment.

1.1 Age

Dose adjustment as a function of individual physiology seems to be more appropriate than adjustment as a function of age.[58] As age increases, physiological alterations may emerge such as hypoalbumin-

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Table III. Toxicity 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	Ref
			neutropenia	leucopenia	thrombocytopenia	anaemia	mucositis	diarrhoea	nausea/vomiting	asthenia	alopecia[b]	neuropathy	pain		
Irinotecan 80-350 90min infusion/FU bolus and/or continuous infusion/FA low dose or high dose	Variable	487	15-64	18	0	0-6	0-9	12-24	9-15	6-7	21-67	NR	1-3 (abdominal)	0	43-45, 46[c]
Oxaliplatin 50-135 2-6h infusion/FU bolus and/or continuous infusion/FA	Variable	442	10-39	9-18	2-13	0-9	0-18	0-53	0-28	NR	19-50	0-28	NR	0-2	47-52
Irinotecan 80 30min infusion/oxaliplatin 85 2h infusion	D1, D8, D15, every 4W/D1, D15, every 4W	36	19	11	6	3	0	19	17	NR	79	8	NR	0	53

a Minimum and maximum percentage found in references.

b Any grade.

c Preliminary results**.**

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

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Table IV. Risk factors for toxicity and implications for optimising the treatment of colorectal cancer

Anticancer agent	Independent risk factor	Dependent risk factor	Effect on toxicity	Toxicity features	Implications for dose individualisation
Fluorouracil	Age > 65-70 years[29,54,55]		Toxicity increase	Leucopenia/mucositis[a]; haematological/nonhaematological, including hand-foot syndrome[b]	Reduction
		Cachexia[56]	Toxicity increase	Neurotoxicity	None/reduction
		Low lean body mass[54]	Toxicity increase	Leucopenia	None/reduction
	Female gender[29,54,55,57]		Toxicity increase	Nonhaematological/hand-foot syndrome; leucopenia/mucositis	Reduction
	Poor performance status[29]		Toxicity increase	Haematological	Reduction
	Good performance status[29]		Toxicity increase	Nonhaematological	None/reduction
	Pharmacogenetics (DPD-polymorphism)[58-63]		Toxicity increase		DPD-deficiency (<0.100 nmol/min/mg protein): contraindicated
	Bolus *vs* CI administration schedule[29]		Toxicity increase	Haematological	
	Bolus *vs* CI administration schedule[29]		Toxicity decrease	Hand-foot syndrome	
	D × 5 *vs* weekly administration schedule[14]		Toxicity increase	Leucopenia	
	D × 5 *vs* weekly administration schedule[14]		Toxicity increase	Mucositis	
	D × 5 *vs* weekly administration schedule[14]		Toxicity decrease	Diarrhoea	
		Circadian timing[64,65]	Toxicity decrease	Mucositis, diarrhoea	
	Previous chemotherapy-related diarrhoea[66]		Toxicity increase	Diarrhoea	No weekly schedule
		Summer season[66]	Toxicity increase	Diarrhoea	
	Xerostomia[67]		Toxicity increase	Mucositis	No D × 5 schedule
	Neutrophils < 4000/mm^3[67]		Toxicity increase	Mucositis	No D × 5 schedule
Raltitrexed	Female gender[54]		Toxicity increase	Transaminase level elevation	Reduction
	Renal impairment[68,69]		Toxicity increase	Haematological/gastrointestinal	CrCl < 25 ml/min: contraindicated; 25 ml/min < CrCl < 65 ml/min: dose × 1/2, interval 4 weeks
	Hepatic impairment[31,32]		Toxicity increase	Transaminase level elevation	Severe impairment: contraindicated
Irinotecan	Age > 65-70 years[33,70]		Toxicity increase	(Late) diarrhoea	Reduction

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Table IV cont.

aemia due to poor nutrition, reduction of hepatic or renal blood flow, influence of comedication, etc.[74] Variations in body composition and especially bodyweight loss may result in modifications of the volume of distribution for lipophilic drugs, and in variations of the plasma exposure as reflected by the area under the curve (AUC). Major pharmacokinetic variability has also been observed for non-lipophilic drugs. Pharmacokinetic variability appears to be increased in the elderly, partly because of glomerular filtration impairment and/or hypoproteinaemia, which can occur in those over 60 years of age.[78]

Zalcberg et al.[54] investigated the relationships between the toxicities of fluorouracil and raltitrexed, and age, cycle number and gender in 439 patients. Approximately 20 to 24% of the patients in each treatment group were aged 70 years or older. Multiple regression analysis revealed that grade 3 and 4 leucopenia and mucositis were significantly correlated with age only for the combination fluorouracil-folinic acid (Mayo Clinic regimen). The incidence of grade 3 and 4 leucopenia was 21% for patients aged under 60 years, 32% for patients aged 60 to 69 years and 40% for patients aged over 70 years, while the incidence of grade 3 and 4 mucositis was 11, 26 and 36%, respectively. For raltitrexed, no significant differences between the age groups with regard to toxicity were observed in this study.

In a meta-analysis of randomised clinical trials comparing fluorouracil continuous infusion with fluorouracil bolus injection, age was found to be an independent prognostic factor for haematological and nonhaematological toxicity and for hand-foot syndrome (palmar-plantar erythrodysesthesia).[29] Moreover, age appeared to be an independent predictor of severe toxicity ($p < 0.001$; univariate analysis) in a multicentre trial of fluorouracil-based chemotherapy. Analysis of toxicity data from 331 patients showed that age 70 years or over was significantly associated with the occurrence of any severe toxicity (58 *vs* 36% for age under 70 years; $p < 0.001$), leucopenia (24 *vs* 10%; $p < 0.005$), diarrhoea (24 *vs* 14%; $p = 0.01$), vomiting (15 *vs* 5%; $p = 0.01$), severe toxicity in more than 2 organ sys-

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Table IV. Contd

Anticancer agent	Independent risk factor	Dependent risk factor	Effect on toxicity	Toxicity features	Implications for dose individualisation
	Performance status > 1[36,71]		Toxicity increase	Neutropenia/diarrhoea	Reduction
	Bilirubinaemia[72,73]		Toxicity increase	Intestinal	Bilirubin > 1.5 × ULN: contraindicated; 1.0 × ULN < bilirubin < 1.5 × ULN: TDM
	Pharmacogenetics (UDPGT1A1-polymorphism)[60,74,75]		Toxicity increase		UDPGT-deficiency (Gilbert's syndrome, Crigler-Najjar type I): contraindicated
	Administration schedule (175 mg/m^2 D1 and D10 or D11, every 3W)[39]		Toxicity decrease		Unknown (preliminary results)
Oxaliplatin	Renal impairment[76]				CrCl < 30 ml/min: contraindicated
		Circadian timing[77]	Toxicity decrease	Neurotoxicity/neutropenia	Preference for chronomodulation

a Mayo regimen.

b Continuous infusion.

CI = continuous infusion; **CrCl** = creatinine clearance; **D** = day; **DPD** = dihydropyrimidine dehydrogenase; **TDM** = therapeutic drug monitoring; **ULN** = upper limit of normal range; **UDPGT** = uridine 5′-diphosphate-glucuronyltransferase; **W** = week.

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tems (10 *vs* 3%; p = 0.02) and treatment-related mortality (9 *vs* 2%; p = 0.01).[55]

The dose-limiting toxicities of irinotecan are delayed diarrhoea (occurring >24 hours after administration) and neutropenia. In a phase II study by Rougier et al.[36] delayed diarrhoea was more frequent and more severe in patients older than 65 years (p = 0.059) and there was a tendency for less frequent grade 3 and 4 neutropenia in patients under 65 years of age.[36] With regard to diarrhoea, this result was confirmed by a study with oral irinotecan, wherein all patients developing grade 4 diarrhoea were 65 years of age or over.[70]

Furthermore, Rothenberg et al.[33] found a significant association between the incidence of delayed diarrhoea and age 65 years or more (p = 0.008) in a multicentre phase II trial with 166 patients when all cycles of administration were examined.[33] For oxaliplatin, no data are available so far with regard to the association between age and toxicity.

1.2 Bodyweight

The main physiological changes that occur in individuals who are overweight that affect drug disposition are alterations in blood volume, cardiac output, lean body mass, organ size and adipose tissue mass.[74] The volume of distribution of anticancer drugs may be different in patients who are overweight. Hepatic drug metabolism is influenced variably: the extent of phase II conjugation increases with bodyweight, while acetylation and oxidation reactions remain unaffected by changes in bodyweight. Furthermore, the effect of bodyweight on renal clearance depends on the fraction of the drug excreted by glomerular filtration.[56]

From the limited data available, it can be concluded that being overweight seems to influence the disposition and elimination of cytotoxic agents. Because being overweight is a common clinical problem, prospective pharmacokinetic studies are needed to show whether increased bodyweight is a risk factor for toxicity.[79]

The influence of cachexia on the pharmacology of anticancer drugs is also not clear as yet. For fluorouracil and folinic acid, patients with malnutrition experienced more neurotoxicity as the clearance of the fluorouracil metabolite was decreased.[56]

No data are yet available on the influence of excess bodyweight and cachexia on the pharmacokinetics of raltitrexed, irinotecan and oxaliplatin.

1.3 Lean Body Mass and Body Composition

Several characteristics of body size have been proposed to be correlated with drug clearance. Among these, lean body mass (LBM) has been suggested to correlate better to drug clearance than body surface area or bodyweight. However, a standard method for determining LBM, which depends on height, bodyweight and age, is not available.[80]

The volume of distribution of hydrophilic drugs correlates very well with LBM, with correlation coefficients of up to 0.9. For lipophilic drugs, the volume of distribution correlates better with bodyweight than with LBM. For drugs eliminated by the liver, especially in patients who are obese, LBM is valuable for calculating maintenance doses because hepatic clearance for these drugs is proportional to LBM.[81]

The influence of body composition on pharmacokinetics has been investigated for several anticancer drugs.[82] These drugs vary widely in terms of hydrophobicity/hydrophilicity and their volume of distribution is therefore influenced more or less by differences in body composition.

In the study of Zalcberg et al.,[54] mentioned in section 1.1, univariate analysis of toxicity and LBM showed a statistically significant relationship between low LBM and grade 3/4 leucopenia for patients receiving fluorouracil-folinic acid (p = 0.009). This significance disappeared on multivariate analysis, suggesting that the univariate effect was caused by gender, as females have a lower LBM than males. A nonsignificant trend was found for the association of mucositis with low LBM for fluorouracil-folinic acid (p = 0.07).[54] However, Fleming et al.[83] reported the fluorouracil clearance to be unaffected by nutritional status in patients with head and neck cancer.

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For raltitrexed, there was a trend ($p = 0.08$) for the association between low LBM and elevated transaminase levels as a measure for hepatic toxicity.[54]

1.4 Gender

Differences in toxicity between men and women may be related to differences in LBM or body composition. In the meta-analysis of trials with different fluorouracil administration schedules, gender appeared to be an independent prognostic factor for grade 3 and 4 nonhaematological toxicity and for hand-foot syndrome, with female patients having a significantly higher risk of toxicity.[29] For haematological toxicity, no difference between the genders was found.

Univariate analysis of toxicity data from the multicentre trial with fluorouracil-based chemotherapy revealed that female gender was an independent predictor of any severe toxicity ($p < 0.0001$). Women experienced an increased incidence of leucopenia ($p < 0.0005$), infection ($p < 0.005$), diarrhoea ($p < 0.01$), multiorgan system toxicity ($p = 0.01$) and vomiting ($p = 0.03$).[55]

A meta-analysis of 6 North Central Cancer Treatment Group (NCCTG) trials involving 731 patients receiving their first fluorouracil-based chemotherapy was undertaken to explore the association of gender with the incidence and severity of stomatitis. Statistic analysis revealed that the incidence of any stomatitis for women was 63% versus 52% for men ($p = 0.002$). The incidence of severe or very severe stomatitis for men and women was 22 and 12%, respectively ($p = 0.0006$). On average, women reported stomatitis with severity roughly 0.4 points higher than men on a 0 to 4 ordinal scale ($p < 0.00001$). Furthermore, women were 11% more likely than men to experience leucopenia of National Cancer Institute (NCI) common toxicity criteria grade >0 (70 *vs* 59%; $p < 0.00001$) and grade >2 (18 *vs* 11%; $p = 0.004$).[84]

In the phase III trial of Zalcberg et al.[54] comparing fluorouracil-folinic acid with raltitrexed, 41% of the 439 patients were female. In the fluorouracil-folinic acid group, female patients experienced significantly more leucopenia grade 3/4 than male patients (39 *vs* 23%, respectively; $p < 0.05$). In the raltitrexed group, significantly more female patients had increases in transaminase levels (16 *vs* 7%, respectively; $p < 0.05$).[54]

A study involving 26 patients revealed that fluorouracil clearance was higher in males than in females.[84] This was confirmed in a larger trial with 380 patients, indicating that a gender difference with regard to fluorouracil toxicity may be due to a lower capacity to clear fluorouracil in women than in men.[85]

In a phase II trial of weekly irinotecan therapy, Rothenberg et al.[33] found no significant association between grade 3/4 events and gender. This was in accordance with the earlier observations of Gupta et al.,[72] who found no difference between either incidence and severity of toxicity based on gender.

1.5 Performance Status

The Eastern Cooperative Oncology Group (ECOG), the World Health Organization (WHO) and Karnofsky performance status scales are widely used to evaluate the functional status of patients with cancer to determine their eligibility for clinical trials and their prognosis. The ECOG and WHO scales range from 0 (normal activity, no complaints) to 4 (completely disabled, 100% bedridden) and the Karnofsky scale ranges from 100 (normal activity, no complaints) to 0 (deceased).[86] Although performance status is influenced by many factors, it can also be taken as an independent prognostic factor.

A meta-analysis of different administration schedules of fluorouracil revealed that performance status was an independent prognostic factor for toxicity.[29] Patients with a poor performance status had a significantly higher risk of haematological toxicity ($p = 0.03$), while patients with a good performance status had a higher risk of nonhaematological toxicity ($p = 0.007$).[29]

In a phase II study with irinotecan, a baseline performance status of >1 on the ECOG scale was a risk factor for the development of grade 3/4 neutropenia and diarrhoea.[36] In another study, performance status was found to be significantly related

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to the percentage decrease of the white blood cell count.[71]

1.6 Renal Function

In patients with renal failure, treatment adjustments are made depending on the agent involved.[58] Guidelines for dose adjustment for impaired renal function are available, although the objective information for many drugs is scarce or even nonexistent. As a result, the existing guidelines are largely empirical.[56]

A deterioration of renal function may cause drug accumulation and increased toxicity. Dose adjustment is usually recommended for drugs that are excreted unchanged or as active metabolites by the kidney by more than one-third if glomerular filtration rate is less than 70% of the normal value.[78]

For fluorouracil, plasma renal clearance accounts for about 5% of total clearance, so dose adjustment is not indicated in patients with renal impairment.[87] 40 to 50% of the administered dose of raltitrexed is excreted unchanged into the urine. Because of the risk of severe haematological and gastrointestinal toxicity, raltitrexed should not be used in patients with renal dysfunction [creatinine clearance (CrCl) <25 ml/min]. In patients with mild to moderate renal impairment (CrCl 25 to 65 ml/min), dose and treatment frequency reduction is recommended.[68,69]

The mean 24-hour irinotecan urinary excretion represents 17 to 25% of the administered dose, while the recovery of the active metabolite SN-38 and its glucuronide in urine represents only 1 to 3%.[88] Therefore, dose adjustment does not seem to be necessary in patients with impaired renal function, although this has not been confirmed by clinical data as yet.

In a study conducted by Massari et al.,[89] oxaliplatin was administered without any pre- or posthydration to patients with normal and impaired renal function, respectively. After a single dose of oxaliplatin 130 mg/m^2, a positive correlation was found between the plasma platinum clearance and renal function. However, the toxicities reported in the 2 groups of patients were similar. To date, no comparative data are available for patients who received repeated cycles of treatment. According to the manufacturer's information, oxaliplatin should not be given to patients with severely impaired renal function (CrCl <30 ml/min).[76]

1.7 Hepatic Function

The (patho)physiological defect underlying abnormal hepatic function values can be primarily hepatocellular, biliary obstructive or mixed. The effect of hepatic impairment on drug clearance therefore depends on the route of elimination of the drug. A parenchymal defect will have most effect on drugs eliminated by biotransformation (e.g. anthracyclines, oxazaphosphorines), whereas an obstructive defect mainly influences the clearance of drugs excreted unchanged by the hepatobiliary route (e.g. vinca alkaloids).[90]

In patients with hepatic failure, dose adjustment may be required for drugs that are hepatically cleared. The guidelines for dose adjustment, however, are largely based on empirical data and are sometimes even conflicting.[56]

For fluorouracil, the liver is considered to be the main organ of elimination. The effect of liver dysfunction as such on pharmacokinetics (i.e. elimination) has not been well studied. Drug bioavailability and disposition, respectively, do not seem to be significantly altered in patients with hepatic dysfunction or hepatic metastases, indicating that no dose adjustment is required in patients with liver impairment.[83,91,92] However, fluorouracil is converted mainly in the liver into 5-fluorodihydrouracil by the enzyme dihydropyrimidine dehydrogenase (DPD). Owing to constitutional differences in enzymatic expression, there is a substantial interindividual heterogeneity in catabolising activity (see section 1.9).[59,93]

Raltitrexed undergoes intracellular polyglutamation, leading to more potent inhibitors of thymidylate synthase than fluorouracil. Furthermore, the polyglutamates are retained within cells longer than raltitrexed and cause enhanced and extended inhibition of thymidylate synthase. Apart from polyglutamation, raltitrexed is not metabolised in the

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liver nor in the other metabolising organs. In a comparative study of 7 patients with mild to moderate hepatic impairment and 8 patients with normal hepatic function the plasma concentration-versus-time profiles in the 2 patient groups were similar.[68] However, significant elevations in transaminase levels (grade III/IV) have been reported in over 10% of patients using raltitrexed. These elevations were more common in patients with abnormal baseline transaminase levels or hepatic metastases. Raltitrexed, therefore, should not be used in patients with severe hepatic impairment, clinically manifest jaundice or a decompensated liver function.[31,32]

Irinotecan is extensively metabolised in the liver into its active metabolite SN-38 by the carboxylesterase enzyme system. SN-38 is mainly glucuronidated by hepatic uridine 5′-diphosphate-glucuronyltransferase (UDPGT). The cumulative biliary excretion is 25% for irinotecan and 1 to 3% for SN-38 and its glucuronide. Certain hepatic parameters have been correlated negatively with irinotecan total body clearance, such as bilirubinaemia and γ-glutamyl transpeptidase.

An additional significant positive correlation between the metabolic ratio of the AUC of SN-38 to the AUC of irinotecan, and the liver function parameters bilirubinaemia, AST and ALT, respectively, was observed. Since the AUC of irinotecan and SN-38 have been correlated significantly with leucopenia and, sometimes, with the intensity of diarrhoea, dose adjustment based on hepatic parameters may improve the therapeutic index.[88,94,95]

Within 3 days of intravenous administration, 50% of oxaliplatin is recovered in urine, whereas faecal excretion is minimal.[96] Hepatic biotransformation seems to be of no or minor importance, i.e. dose adjustment in patients with liver impairment is not required.

1.8 Serum Albumin and Bilirubin

Acidic and basic drugs tend to bind to albumin and α1-glycoprotein, respectively. Hypoalbuminaemia caused by liver impairment, nephrotic syndrome, malabsorption or malnutrition can significantly decrease the extent of plasma binding, which is clinically relevant for those drugs that are at least 90% protein-bound.[90]

A subnormal serum albumin level will increase the unbound fraction of highly bound drugs. As bilirubin is also bound to albumin, an increased serum bilirubin level can displace the drug from albumin by competition, and again increase the unbound fraction. In both situations, the result is an increase in systemic exposure, i.e. AUC, of the active drug. Moreover, increased serum bilirubin is frequently associated with liver impairment, which decreases the clearance of total as well as unbound drug. In conclusion, it is very complicated to predict the net effect of hypoalbuminaemia, hyperbilirubinaemia and/or liver impairment on the pharmacokinetics of highly bound drugs.[97,98]

A study of prognostic factors for the toxicity of fluorouracil in 130 patients revealed that baseline serum albumin was not predictive for toxicity.[99] Since fluorouracil is only 10% protein-bound, this result was to be expected.[100]

Although 93% of raltitrexed is bound to plasma proteins, no data are available on the effect of low albumin levels or high bilirubin levels on pharmacokinetics and/or toxicity parameters.[101]

The plasma protein binding for irinotecan and SN-38 is 65% and 95%, respectively.[88] Decreased glucuronidation of SN-38 to the inactive SN-38 glucuronide can lead to accumulation of active metabolite and enhanced biliary excretion of SN-38. This biliary excretion has been suggested to determine the severity of diarrhoea, the dose-limiting toxicity of irinotecan.[60,102] In a study of 40 patients, grade 3 or 4 intestinal toxicity was associated with significantly higher values of the biliary index (BI) than grade 0 to 2 toxicity ($p < 0.001$); the BI being defined as the product of the AUC of irinotecan and the ratio of the AUCs of SN-38 to SN-38 glucuronide (biliary ratio).[72] Because glucuronidation of SN-38 and conjugation of bilirubin are catalysed by the same isoenzyme, UDPGT-1A1, unconjugated serum bilirubin may be predictive for irinotecan toxicity.[74] For irinotecan, significant correlations have been observed between bilirubinaemia and total body clearance and

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metabolic ratio, respectively (see section 1.7). As a result, administration of irinotecan is contraindicated in patients with a bilirubin >1.5 times the upper limit of the normal range (ULN), and in patients with bilirubin 1.0 to 1.5 times the ULN, monitoring of serum concentrations is recommended.[73]

Approximately 85% of plasma oxaliplatin rapidly becomes protein-bound. The proportion of protein-bound platinum increases with time to 95% at 5 days after administration. At equilibrium, about 50% of oxaliplatin is bound to red blood cells. Red blood cell platinum from oxaliplatin is not exchangeable into plasma and it accumulates with a mean half-life consistent with that of erythrocytes. Oxaliplatin does not accumulate in plasma, which explains the reversibility of the dose-limiting neurotoxicity.[96,103] The impact of low albumin and high bilirubin levels on the pharmacokinetics of oxaliplatin is not known.

1.9 Pharmacogenetics

Drug metabolism is a major determinant of variability in the pharmacokinetics of anticancer drugs, which is frequently due to polymorphism in the genes for drug-metabolising enzymes, i.e. genetic polymorphism.[60]

Pharmacogenetic phenotyping is not frequently carried out in clinical practice as yet, although for some anticancer drugs, such as fluorouracil, its clinical relevance has been proven.[90] Phenotyping may therefore be a potential target for therapeutic drug monitoring of several other anticancer drugs.[90]

Genetic polymorphism has been characterised for fluorouracil detoxicification by DPD.[58] DPD catalyses the initial rate-limiting step in the catabolism of fluorouracil to dihydrouracil. Patients who lack this enzyme will have an 80 to 90% reduction in fluorouracil clearance and this has been associated with severe toxicity of the drug in several reports.[58-62] In a population study by Etienne et al.,[63] a significant DPD deficiency (<0.100 nmol/min/mg protein) was found in only 3% of patients. Therefore, it was concluded that pretreatment determination of DPD activity is not a useful indicator for dose individualisation, although the identification of severe DPD deficiency could warrant using a decreased starting dose or even using an alternative chemotherapy regimen.[63] On the other hand, the introduction of potent inhibitors of DPD may facilitate effective treatment with small oral doses of fluorouracil.[104,105]

Raltitrexed is converted intracellularly by the enzyme folylpolyglutamyl synthase (FPGS) to cytotoxic polyglutamates. Genetic polymorphism of FPGS has been suggested to be related to the high number of drug-related deaths in the raltitrexed group in the recently suspended Pan European Trial in Adjuvant Colon Cancer-1 (ETACC-1) trial.[106,107] Another hypothesis is that the raltitrexed toxic deaths may be associated with patients with a lower CrCl, i.e. impaired renal function. Although genetic polymorphism could contribute to variations between individuals in sensitivity to raltitrexed, confirmatory studies are needed for the identification of pharmacogenetics as a risk factor for adverse effects.[106,107]

For irinotecan, variability in glucuronidation may be toxicity-related (see section 1.8). The high interpatient variability of irinotecan and SN-38 pharmacokinetics may be due to genetic polymorphism of UDPGT-1A1, the UDPGT isoenzyme responsible for the metabolism of SN-38.[108] Further knowledge of the metabolic mechanism is required to assess the possible consequence for dose individualisation.[88] Anyhow, patients with Gilbert's syndrome and Crigler-Najjar type I syndrome, characterised by a UDPGT deficiency, are at increased risk of toxicity and should, therefore, be excluded from irinotecan therapy.[60,74,75]

The main activation pathways of oxaliplatin are reactions with plasma bicarbonate and with intracellular bicarbonate and phosphate. Inactivation occurs mainly by reactions with strong nucleophiles. Since the major activation and inactivation routes do not require (extra)hepatic enzymes, pharmacogenetic factors are unlikely to play a role in interpatient pharmacokinetic variability.[96,109]

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1.10 Drug Administration Schedule

The toxicity of anticancer agents have shown to be dependent on the drug administration schedule. The toxicity profiles of fluorouracil and folinic acid are significantly associated with cycle number and drug administration schedule. As is shown in tables I, the most commonly used administration schedules have different toxicity profiles. In a meta-analysis of randomised trials based on individual data from 1219 patients, haematological toxicity was observed more frequently with fluorouracil bolus than with fluorouracil continuous infusion (31 and 4% respectively; $p < 0.0001$). Hand-foot syndrome was less frequent with fluorouracil bolus than with fluorouracil continuous infusion (13 and 34%, respectively; $p < 0.0001$).[29]

In a study of 7 fluorouracil-based treatment regimens[13] 3 were schedules which involved the combination of fluorouracil with folinic acid: (i) fluorouracil bolus with low dose folinic acid (5 days, every 4 to 5 weeks; n = 85); (ii) fluorouracil bolus with high dose folinic acid (once a week for 6 weeks, followed by 2 weeks rest for each 8-week cycle; n = 85); and (iii) fluorouracil continuous infusion with low dose folinic acid (days 1 to 28 of a 5-week cycle; n = 81). As in the meta-analysis,[29] this study showed that more severe haematological toxicity was associated with the rapid intravenous than with the continuous infusion arm of the study.[13] Diarrhoea occurred most frequently in the once a week for 6 weeks arm compared with the every 5 days or the continuous infusion arm. Although a statistical comparison was not made in this study, the results are indicative of administration schedule–dependent toxicity.[13]

In a large multicentre trial, the toxicity profiles of fluorouracil 425 mg/m^2 bolus plus folinic acid 20 mg/m^2 (daily for 5 days with courses repeated every 4 to 5 weeks; n = 183) and fluorouracil 600 mg/m^2 bolus plus folinic acid 500 mg/m^2 (weekly for 6 weeks with courses repeated every 8 weeks; n = 179) were compared. Differences were significant ($p < 0.01$) for severe leucopenia (29% for the daily regimen *vs* 5% for the weekly regimen), grade 3/4 mucositis (24% for the daily regimen *vs* 2% for the weekly regimen) and grade 3/4 diarrhoea (18% for the daily regimen *vs* 32% for the weekly regimen).[14]

In summary, bolus injection of fluorouracil is associated with a higher risk for haematological toxicity than continuous infusion, whereas hand-foot syndrome is less frequent with bolus injection. Moreover, leucopenia and mucositis are observed more frequently with intensive courses of therapy using daily for 5-day administration than with weekly administration, whereas diarrhoea is more frequent with weekly administration.

Phase III clinical trials with raltitrexed only evaluated an administration schedule of 3 mg/m^2 once every 3 weeks, so a comparison between different schedules in terms of toxicity patterns is not possible.[30-32]

For irinotecan the phase II recommended dosages were 240 to 350 mg/m^2 every 3 weeks and 100 to 150 mg/m^2 per week.[33-38] Owing to a lack of data from comparative studies, no conclusions can be drawn with regard to differences in toxicity. Based on the results available, there seems to be no major difference between these schedules in the severity and frequency of the dose-limiting toxicities diarrhoea and leucopenia.[33-38] Recently, however, preliminary results were presented of a comparison of irinotecan 350 mg/m^2 every 21 days and a new schedule of irinotecan 175 mg/m^2 on days 1 and 10 or 11 every 21 days.[39] Analysis of the results indicates that administration of the same total dose of irinotecan divided into 2 doses every 21 days yields similar efficacy but a lower incidence of toxicity (see table II).

In phase I trials, oxaliplatin was administered in different doses by short infusion (1 to 12 hours) and by (chronomodulated) continuous infusion.[96] With short infusion, as with continuous infusion, the dose-limiting toxicities are neutropenia and peripheral neuropathy. A direct comparison has been made only between constant and circadian rhythm-modulated infusion (see section 1.11). The total cumulative dose is considered to be more predictive for toxicity than is the maximum tolerated dose. Based on the estimated cumulative levels, the cur-

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rently recommended dosage schedules are 130 mg/m^2 given over 2 hours every 3 weeks and 125 to 150 mg/m^2 given as a chronomodulated intravenous infusion over 5 consecutive days every 3 weeks.[96]

1.11 Circadian Timing

Some anticancer agents show circadian changes in their pharmacokinetics. A circadian rhythm in the plasma concentration was demonstrated for fluorouracil administered as a continuous infusion for 5 days, which may be correlated to altering DPD activity. Harris et al.[110], found a 5-fold variation in plasma fluorouracil concentration during continuous infusion. The decrease of fluorouracil concentration during the night time appeared to be related to an increase in DPD activity, and vice versa during day time. As a consequence, with the availability of programmable pumps, information on the circadian pattern of fluorouracil and DPD may be useful for planning infusion schedules in order to maintain an optimal plasma drug concentration over a 24-hour cycle.[110-112]

A study of fluorouracil and oxaliplatin by Metzger et al.[64] indicated that chronomodulation by adapting continuous infusion rates of fluorouracil to plasma concentrations may decrease mucosal toxicity and, therefore, may permit dose escalation. Giacchetti et al.[113] found that a 6-hour infusion of oxaliplatin 125 mg/m^2 added significant activity to chronomodulated fluorouracil-folinic acid as first-line chemotherapy for metastatic colorectal cancer, with acceptable toxicity.[113] In addition, preliminary results from Bochicchio et al.[65] showed the reversibility of toxicity by using a chronomodulated schedule in patients who previously had to stop therapy with continuous infusion of fluorouracil at a constant rate for toxicity reasons (mucositis, diarrhoea).

For irinotecan, a pilot study has been performed, with success, into the feasibility of chronomodulated delivery of the drug.[114] This study is now being continued as a comparative trial of chronomodulated versus standard infusion.

Caussanel et al.[77] studied the toxic effect of 5-day administration of oxaliplatin by constant infusion (12 evaluable patients) or circadian rhythm-modulated infusion (11 evaluable patients). Mild and severe neurotoxicity were observed more frequently with the constant than with the chronomodulated infusion (28 *vs* 2% of cycles, respectively; $p < 0.001$). Also, the incidence of neutropenia grade ≥2 was lower with the circadian-modulated schedule (2 *vs* 19%; $p < 0.05$).[77] In the meantime, several circadian-modulated schedules have been developed to obtain higher concentrations of oxaliplatin and to reduce dose-limiting toxicity.[115-120]

1.12 Other Risk Factors

The Italian Group for the Study of Digestive Tract Cancer evaluated different factors that might influence fluorouracil-induced diarrhoea. They found that a history of previous episodes of chemotherapy-related diarrhoea ($p < 0.00005$) and summer season ($p < 0.014$) to be significant risk factors for developing diarrhoea. Therefore, patients who have experienced diarrhoea in earlier courses of chemotherapy should be carefully monitored.[66] Although patients may be at higher risk for fluorouracil-induced diarrhoea during summer, seasonal dose adjustment is not likely to be indicated.

The results of another study of risk factors associated with mucositis in 63 patients receiving fluorouracil showed that xerostomia at baseline, xerostomia during chemotherapy and lower baseline neutrophil levels were significant predictors of oral mucositis. As a result, in patients with xerostomia or low neutrophil levels, a dose schedule with a low frequency of mucositis can be recommended, i.e. a weekly schedule.[67]

1.13 Drug-Drug Interactions

The drug interactions of fluorouracil and irinotecan are summarised in table V. The main drug-drug interactions that have been described for fluorouracil are the interactions with the anticancer drugs cyclophosphamide and methotrexate, and interactions with folinic acid, interferon-α, allopurinol, dipyramidol, metronidazole, cimetidine and warfarin.[121-127] Of these interactions, interferon-α, methotrexate and folinic acid are added to fluoro-

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Table V. Drug interactions for fluorouracil and irinotecan and their implications for dose individualisation in the treatment of colorectal cancer

Anticancer agent	Drug-drug interactions	Effect	Implications for dose individualisation
Fluorouracil	Allopurinol	AUC of FU increased; MTD of FU increased	TDM for FU/avoid allopurinol
	Dipyramidol	AUC of FU increased; Vd of FU increased	TDM for FU/avoid dipyridamol
	Metronidazole	Cl of FU decreased and toxicity increased	TDM for FU/avoid metronidazole
	Cimetidine	AUC of FU increased	TDM for FU/avoid cimetidine
	Warfarin	PTT increased	Dose adjustment for warfarin based on PTT
Irinotecan	Valproic acid (sodium valproate)	AUC of SN-38 increased (data in rats)	Unknown
	Phenobarbital (phenobarbitone)	AUC of irinotecan and AUC of SN-38 decreased (data in rats)	Unknown
	Cyclosporin	Cl of irinotecan decreased (data in rats)	Unknown

AUC = area under the concentration-time curve; **Cl** = clearance; **FU** = folinic acid; **MTD** = maximum tolerated dose; **PTT** = prothrombin time; **SN-38** = active metabolite of irinotecan; **TDM** = therapeutic drug monitoring **Vd** = volume of distribution.

uracil deliberately to enhance efficacy. Cyclophosphamide is not used in the treatment of colorectal cancer.

Allopurinol inhibits oxipurinol orotate phosphoribosyltransferase, resulting in a decreased formation of fluorodeoxyuridine monophosphate and fluorouracil triphosphate. Coadministration of allopurinol increases the maximum tolerated dose and AUC of fluorouracil and can diminish granulocytopenia produced by bolus doses of fluorouracil.[121,122]

Dipyridamol 7.7 mg/kg/day was found to increase fluorouracil clearance or volume of distribution at steady-state by 30%.[123]

When fluorouracil bolus given daily for 5 days is combined with a metronidazole bolus given daily for 5 days, the toxicity of fluorouracil increases due to a 27% reduction in the clearance of fluorouracil, whereas cytotoxicity is not modified.[124]

Pretreatment with cimetidine for 4 weeks resulted in higher peak plasma concentrations and AUC of fluorouracil, which may be caused by hepatic enzyme inhibition and reduced hepatic blood flow.[125]

Fluorouracil has been shown to increase bleeding time and prothrombin time in patients receiving warfarin therapy. Several patients have been described with more or less severe morbidity and prolonged hospitalisation caused by this interaction.[126]

Raltitrexed has been found not to displace warfarin from its plasma protein binding site *in vitro*, although 93% of raltitrexed is bound to plasma proteins.[101] Because of the active tubular secretion of raltitrexed contributing to its renal clearance, a potential interaction with similarly excreted drugs, such as nonsteroidal anti-inflammatory drugs, cannot be excluded. However, during clinical trials, such an interaction has not been observed.

There have been some studies in rats to evaluate the drug interactions of irinotecan with other drugs. Valproic acid (sodium valproate), an inhibitor of glucuronidation, appeared to block the glucuronidation of SN-38 and increased the AUC of SN-38, whereas irinotecan pharmacokinetics remained unchanged. Phenobarbital (phenobarbitone) pretreatment was shown to reduce both the AUC of SN-38 and the AUC of irinotecan, probably by inducing UDPGT activity.[128] Cyclosporin administered to rats reduced irinotecan clearance by decreasing biliary excretion.[129]

In humans, the simultaneous administration of fluorouracil-folinic acid during chemotherapy with irinotecan showed no substantial effects on the metabolism and pharmacokinetics of irinotecan.[130] Also, the biotransformation rate of irinotecan into SN-38 was not significantly changed by adding fluorouracil-folinic acid.[130]

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Preliminary data from a study by Lokiec et al.[131] suggested a positive pharmacokinetic interaction between irinotecan and oxaliplatin. The AUCs of irinotecan and SN-38 measured in this study after coadministration of irinotecan and oxaliplatin were as high as the AUCs found after monotherapy with irinotecan at 80 to 130% higher dosages. In contrast, Wasserman et al.[132] recently reported similar pharmacokinetic results for coadministered irinotecan and for oxaliplatin to those obtained from previous studies when the drugs were used as single agents.

Fluorouracil is assumed not to modify oxaliplatin pharmacokinetics since fluorouracil does not influence the pharmacokinetics of cisplatin and carboplatin, fluorouracil is poorly bound to plasma proteins and its metabolism is very different from that of oxaliplatin.[103]

Several combinations of fluorouracil, raltitrexed, irinotecan and oxaliplatin have been or are currently being investigated in clinical studies.

2. Implications of Risk Factors for Dosage Individualisation

The risk factors that influence toxicity discussed in section 1 are summarised in tables IV and V. The question remains as to what individual preventive measures should be taken in the presence of one or more risk factors in order to prevent toxicity. Currently, in clinical practice, dosage reduction or extension of the dosage interval are utilised when substantial toxicity has been experienced. This approach cannot prevent severe toxicity occurring in some patients (tables I, II and III). As a consequence, adjusting the dosage before initial treatment, considering relevant individual risk factors is likely to improve the therapeutic index and quality of life. The percentage dose reduction that is most appropriate for dose individualisation is unknown, but in general a 10 to 50% reduction in patients experiencing toxicity is used, depending on the nature and degree of toxicity, the treatment centre and/or the physician. Therefore, the optimal dose adjustment for toxicity control, which is largely dependent on pharmacokinetics, has to be determined in prospective trials.

3. Predictive Value of Pharmacokinetics for Toxicity

Several studies have been performed to investigate the relationship between pharmacokinetic and pharmacodynamic parameters of the drugs discussed in this article. The results of pharmacokinetic studies in relation to toxicity, published between 1980 and March 2000 (MEDLINE, Embase), are shown in table VI. These data demonstrate that pharmacokinetics can be predictive for toxicity. For fluorouracil, some studies[139,152,153] have revealed that individual dose adjustment based on pharmacokinetic parameters leads to reduced toxicity and/or enhanced efficacy. Santini et al.[152] prospectively validated the relationship, found earlier by their group,[134] between elevated AUC values (>30 mg/L•h) of fluorouracil and the frequency of cycles in which signs of toxicity were observed (n = 89). Subsequently, the individual AUC was estimated midway through a 5-day course in 81 patients to decide whether dose reduction during the second half of the cycle was required in order to achieve a target AUC. This resulted in a significant decrease in the incidence of toxic cycles (> grade 2: 12.4 *vs* 20% of patients, $0.02 < p < 0.05$) and higher complete response rates (47 *vs* 31% of patients, $0.02 < p < 0.05$).[152]

In a dose-escalation study, Gamelin et al.[138] defined a therapeutic range for fluorouracil plasma concentrations from 2000 to 3000 μg/L ($AUC_{0\text{-}8h}$: 16 to 24 mg/L•h) for a weekly regimen. In a subsequent study in 152 patients, the initial dose of fluorouracil was adapted weekly according to individual fluorouracil plasma concentrations to reach this therapeutic range. In comparison with the results previously reported with weekly fluorouracil schedules, dosage adjustment with pharmacokinetic monitoring provided a high response rate and long overall survival with a low incidence of toxicity.[139]

In a randomised designed study, Fety et al.[153] made a direct comparison between the effects of a standard dose of fluorouracil (standard arm: n = 57) and an individual dose-adjusted to the $AUC_{0\text{-}48h}$ [pharmacokinetic (PK) arm: n = 49]. In the standard arm, grade 3/4 neutropenia and thrombocyto-

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Table VI. Relationship between pharmacokinetics and toxicity of anticancer agents used in advanced colorectal cancer

Agent	Dosage schedule	No. of patients	Pharmacokinetic parameter	Predictive value for toxicity	References
Fluorouracil	1g IV/hepatic intra-arterial weekly	9	Cl, AUC	Myelosuppression	133
	1000 mg/m^2/day continuous infusion	29	AUC	>30 mg/L•h: mucositis/diarrhoea/myelosuppression	134
	800-1000 mg/m^2 continuous infusion hepatic intra-arterial	16	AUC	>30 mg/L•h: mucositis/diarrhoea/myelosuppression	135
	650-1300 mg/m^2 continuous infusion IV	26	AUC	>30 mg/L•h: mucositis/diarrhoea/myelosuppression	135
	7.5-15 mg/m^2/day × 5 continuous infusion[a]	24	Css	>1.5 μmol/L: leucopenia	136
			Clss	Leucopenia-group: significantly lower Clss	136
	190-600 mg/m^2/day continuous infusion	19	Cl, Css, AUC_{72h}	>WHO grade 2-toxicity group: significant lower Cl, higher AUC_{72h} and Css	137
	185-3600 mg/m^2/day × 3 continuous infusion	42	Css	% frequency mucositis = 100(1-e$^{0.122Css}$), r2 = 0.80	123
				% reduction WBC = 100(1-e$^{0.060Css}$), r2 = 0.61	123
	1000-2000 mg/m^2 W 8h infusion	40	C	>3000 μg/L: acute toxicity	138
			AUC	>24 mg/L•h: acute toxicity	138
	1300 mg/m^2 W 8h infusion initial (with dosage adjustment)	152	C	>3000 μg/L: acute toxicity	139
	500-720 mg/m^2 W bolus	21	AUC	% risk of toxicity ? grade 1 = 1/(1+e$^{[\alpha-\beta logAUC]}$)	140
	750 mg/m^2/day × 5 continuous infusion	21	Cl decrease by interferon-α	>20% reduction *vs* <20% reduction: incidence diarrhoea × 4	141
				>20% reduction *vs* <20% reduction: incidence mucositis grade 3/4 33% *vs* 11%	141
	640 mg/m^2/day 120h continuous infusion	89	$C_{afternoon}$	High $C_{afternoon}$ correlates with worse leucopenia (p = 0.04) and severity mucositis (p = 0.04)	142
	500 mg/m^2/day × 5 continuous infusion	39	C_{mean}	Correlation with haematological toxicity grade (p = 0.001), mucositis grade (p = 0.005), digestive toxicity grade (p = 0.05)	143
Raltitrexed	No data available				
Irinotecan	145 mg/m^2, W × 4, 2W rest	40	BI = AUC irinotecan • AUC SN-38 glucuronide	>4.600 ng•h/ml: intestinal toxicity; >WHO grade 2-toxicity group: significantly higher BI	72
	100-175 mg/m^2, W × 4, 2W rest	21	BI	>WHO grade 2-diarrhoea group: significantly higher BI	102

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Table VI. Contd

Agent	Dosage schedule	No. of patients	Pharmacokinetic parameter	Predictive value for toxicity	References
	350 mg/m^2, every 3W	47	AUC irinotecan and AUC SN-38	% decrease in neutrophil count	94
	125-150 mg/m^2, W × 4	43	AUC SN-38 week 3	Severity of diarrhoea	34
	100-750 mg/m^2, every 3W	64	AUC irinotecan, AUC SN-38	% decrease in WBC count and neutrophil count, grade 2 diarrhoea, nausea, vomiting	144
	60-80 mg/m^2, days 1, 8, 15 × 4-6[b]	11	AUC SN-38 day 1	Platelet nadir	145
			AUC irinotecan and AUC SN-38	Diarrhoea	145
	100-345 mg/m^2, every 3W	32	AUC SN-38	% change in neutrophil count = $(100 \times AUC^{0.7})/(0.51 + AUC^{0.7})$	146
	50-145 mg/m^2 W	59	AUC irinotecan and AUC SN-38	Intensity diarrhoea, % decrease in WBC and neutrophil counts	147
	60-90 mg/m^2, days 1, 8, 15 every 4W[c]	25	AUC irinotecan and AUC SN-38	Severity of diarrhoea	148
			AUC irinotecan	Nadir leucocyte count	148
	100 mg/m^2, W × 4	36	AUC irinotecan, AUC SN-38	Incidence of diarrhoea	71
			AUC irinotecan	% decrease in WBC count	71
	33-750 mg/m^2:	107	AUC irinotecan, AUC SN-38	% decrease in WBC and neutrophil counts	149
	Daily × 3, every 3 W/W × 3/every 3 W		AUC irinotecan, AUC SN-38	Intensity diarrhoea, nausea and vomiting	149
			Cl irinotecan	% decrease in WBC count and neutrophil count (negative correlation)	149
			Cl irinotecan	Intensity diarrhoea, nausea and vomiting (negative correlation)	149
	80-90 mg/m^2, days 1, 8 and 15	23	C_{max} SN-38	Severity diarrhoea	150
			C_{max} 1.75h after start	>12.4 ng/ml: grade 3/4 diarrhoea	150
	33-115 mg/m^2/day × 3, every 3 W	46	AUC irinotecan	Diarrhoea grade	151
Oxaliplatin	130 mg/m^2, every 3 W	16	RBC platinum levels	Anaemia: significantly higher RBC levels day 8, 15, 22	103

a Coadministration with thymidine.

b Coadministration with cisplatin.

c Coadministration with etoposide.

AUC = area under the concentration-time curve; **BI** = biliary index; $\mathbf{C_{afternoon}}$ = concentration in the afternoon; **Cl** = clearance; **Cl**ss = clearance at steady-state; $\mathbf{C_{max}}$ = maximum concentration; $\mathbf{C_{mean}}$ = mean concentration ; **C**ss = concentration at steady-state; **D** = day; **H** = hour; **IV** = intravenous; **RBC** = red blood cell; **SN-38** = active metabolite of irinotecan; **W** = week(ly); **WBC** = white blood cell.

penia occurred significantly more frequently than in the PK arm (17.5 *vs* 7.6%, respectively; p = 0.013). Furthermore, 5.1% grade 3/4 mucositis was observed in the standard arm and none in the PK arm (p < 0.01). The objective response rate between the arms was comparable.[153]

The results from these studies emphasise the clinical significance and benefits of therapeutic drug monitoring for toxicity control and encourage the extension of clinical studies to include dosage individualisation.

4. Discussion

To date, dosage calculation for anticancer drugs has been based on the estimated body surface area of the individual patient, as is done in the search for the maximum tolerated dose of new agents in phase I trials. The body surface area is assumed to be more indicative of the clearance of the individual patient in order to reduce toxicity and improve efficacy in comparison with a dosage calculation based only on bodyweight. Currently, the validity of this approach is being questioned.[80] Calculation of dosage based on body surface area might be 'pseudo'-accurate as the toxicity of anticancer drugs is still a major problem and it is potentially invalidating or even life-threatening. The necessity of toxicity control may be underlined by the fact that in clinical trials, and subsequently in clinical practice, an incidence 33% for dose-limiting toxicity (> NCI common toxicity criteria grade 2) is frequently exceeded (see tables I, II and III). This level is considered to be a threshold percentage for assessing the recommended dosage in phase I studies.[154]

Therefore, until drugs are introduced that have a higher therapeutic index, it will be necessary to search for more adequate predicting factors with respect to toxicity.

In this review, several risk factors that relate to pharmacokinetics have been described which determine chemotherapeutic toxicity in patients with colorectal cancer. The information available in the literature is fragmented and often, particularly for the new cytotoxic agents, incomplete. This, along with the increasing concern for patients' quality of life, necessitates performing further prospective studies on risk factors. Yet we should keep in mind that, in general, the coefficient of a correlation between a pharmacokinetic parameter and efficacy does not exceed 0.7. This means that only half of the variability of tumour response can be explained by drug distribution and elimination and that the other half depends predominantly on the cellular and molecular determinants.[58] However, regarding toxicity, dose individualisation of fluorouracil based on pharmacokinetic parameters has been proven to be beneficial. In fact, the results of these trials are most stimulating for further investigations of toxicity control by therapeutic drug monitoring using the AUC as a leading parameter.

In addition to therapeutic drug monitoring, dose adaptation based on knowledge of risk factors for toxicity is more appropriate for individualising chemotherapy than just calculating the dose based on body surface area. For fluorouracil, age, gender, performance status, history of previous chemotherapy-related diarrhoea, xerostomia, low neutrophil levels, circadian rhythm of plasma concentrations and drug-drug interactions seem to be the factors that have to be taken into consideration when determining the individual dose or dose schedule. Moreover, with unexpected fluorouracil toxicity, exclusion of DPD deficiency is advised. Similarly, for irinotecan, assessing the UDPGT-1A1 activity can be recommended when severe toxicity is experienced. Other significant factors for irinotecan toxicity are age, performance status, bilirubinaemia and administration schedule.

For raltitrexed, gender and renal and hepatic impairment are the most significant critical factors. Oxaliplatin should not be used in patients with severe renal impairment, while the circadian rhythm of oxaliplatin plasma concentrations is a target for dose optimisation.

Future studies may reveal additional data about risk factors, which will lead to an advancement in the identification of patients at risk for toxicity. However, the data currently available can be used for toxicity control in individual patients with colorectal cancer. The definite benefits of the imple-

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menting current knowledge of risk factors in terms of improving the therapeutic index and quality of life for patients with colorectal cancer have yet to be determined.

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