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Chemotherapy for patients with colorectal cancer. Potential contributions by the clinical pharmacist

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For over 40 years, 5-fluorouracil, frequently combined with folinic acid, has been the main cytotoxic drug for the treatment of colorectal cancer. In the last decade, however, new cytotoxic agents have been introduced: raltitrexed, irinotecan, oxaliplatin, and oral analogues of 5-fluorouracil, i.e. tegafur in combination with uracil (UFT) and capecitabine. In addition, novel biologically targeted therapeutics, i.e. angiogenesis inhibitors (e.g., bevacizumab), epidermal growth factor receptor (EGFR)-inhibitors (e.g., cetuximab), farnesyl transferase inhibitors, cell-cycle-interacting agents, nonsteroidal antiinflammatory drugs, immunotherapy, and gene therapy are clinically evaluated, for both single-agent and combination strategies.[1] At present, mainly 5-fluorouracil combined with folinic acid, or capecitabine, with or without irinotecan and/or oxaliplatin are chosen for treatment of colorectal cancer in clinical practice. The use of these agents is increasing due to the addition of second- and even third-line chemotherapy for metastatic colorectal cancer in case of disease progression under first-line and second-line treatment, respectively. Also, adjuvant chemotherapy may be applied for treatment of Dukes' B or stage II colon cancer as well, next to Dukes' C or stage III colon cancer.[2,3] Finally, elderly patients with colorectal cancer are not to be excluded any longer from chemotherapy, since elderly patients benefit to the same extent as younger patients from treatment with cytotoxic agents.[4]

Better systemic chemotherapy has considerably improved prognosis. The median duration of survival among patients with metastatic colorectal cancer increased from 8 months without chemotherapy to 12 months with 5-fluorouracil. The availability of irinotecan and oxaliplatin, next to 5-fluorouracil, further extended the median survival to 21 months.[5] However, treatment with different combinations of these agents is still associated with substantial toxicity.

Currently, the dosage of cytotoxic agents for an individual patient is calculated from the estimated body surface area of the patient, in contrast to the novel biologicals that are applied in fixed doses. Toxicity, however, frequently necessitates decreasing the dosage, extending the dose interval or even discontinuing treatment. Therefore, along with the increasing concern for quality of life, prevention and management of chemotherapy induced toxicity is of major clinical importance.

Risk factors with predictive value for toxicity have been found in several studies. These risk factors are often determined by the pharmacokinetic and pharmacodynamic properties of the drug. In chapter 1, the risk factors for toxicity of the cytotoxic agents 5-fluorouracil, raltitrexed, irinotecan and oxaliplatin in the treatment of advanced colorectal cancer are considered. An analysis of toxicity data of different dose regimens of these agents is also included, since the toxicity profile of cytotoxic agents is known to be dependent on the drug administration schedule used.

For 5-fluorouracil, age, gender, performance status, genetic polymorphism of dihydropyridine dehydrogenase (DPD), drug administration schedule, circadian rhythm of plasma concentrations, history of previous chemotherapy-related diarrhea, 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 (UDPGT-1A1), and drug administration schedule have been shown to be related to irinotecan toxicity. The 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, that has been shown to be effective in controlling the toxicity of 5-fluorouracil in some studies.

Future research is warranted to assess the potential advantage of dose individualisation of chemotherapy founded on risk factors, next to or 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. When this concept appears to be suitable for implementation in clinical practise, the clinical pharmacist may play a vital role in dose individualisation based on risk factors.

In order to reduce toxicity, identification and management of toxicity signs at their first appearance are needed, especially with the introduction of several combinations of 5-FU, raltitrexed, irinotecan and oxaliplatin, in numerous dosing schedules, leading to different toxicity profiles. Therefore, toxicity management should be individualized to anti-cancer agent(s), dosage schedule and patient. Therapeutic drug monitoring of 5-fluorouracil and chronomodulation of 5-fluorouracil and oxaliplatin have been shown to limit toxicity in clinical trials. However, these concepts are not implemented in clinical practice yet.

To date, dose adjustment and intensive supportive measures are the main tools for toxicity control in the treatment of colorectal cancer. Therefore, in chapter 2, supportive measures to prevent or alleviate toxicity symptoms of 5-fluorouracil, raltitrexed, irinotecan and oxaliplatin in the treatment of colorectal cancer, are considered, based on study results. The main toxicity 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 non-pharmacological methods. In addition, guidelines for dosage adjustments when toxicity occurs are presented. These recommendations and guidelines are based on data from clinical trials, manufacturer's guidelines for dosage adjustment, and guidelines from expert panels and associations of oncologists.

For optimal toxicity management, patients should be considered individually, while patients, nurses and physicians should co-operate to identify and treat toxicity symptoms in an early stage of their development.

Dose adaptation based on pharmacokinetic parameters has been shown to decrease the toxicity of some 5-fluorouracil-based continuous infusion regimens. However, 5-FU is frequently administered by bolus injection or short infusion. One of the most common treatment regimens currently in use is the Northern Central Cancer Treatment Group (NCCTG)-Mayo Clinic regimen: 20 mg/m² folinic acid + 425 mg/m² 5-FU bolus or short infusion for 5 consecutive days, every 4 to 5 weeks. In a prospective study, the relationship between 5-fluorouracil pharmacokinetics in plasma and in saliva, and toxicity was investigated in 40 patients receiving the combination of 5-fluorouracil and folinic acid according to the Mayo-regimen.(chapter 3)

The overall non-hematological and hematological toxicity, appeared not to be statistically significant related to the area-under-the-curve in plasma (AUC_p) or in saliva (AUC_s), nor to the maximum concentration measured in plasma (C_{maxp}) or in saliva (C_{maxs}). This also applies to the maximum mucositis grade only. Although statistically significant, the correlation between the AUC_p and AUC_s was relatively low, implying that salivary pharmacokinetics are not accurately predictive of plasma pharmacokinetics. Based on this results, pharmacokinetic parameters do not seem to be adequately predictive for overall toxicity nor for oral mucositis only. Therefore, the application of pharmacokinetic parameters is not appropriate for identification of patients at risk for developing toxicity from treatment with 5-fluorouracil according to the Mayo-regimen. At the present time, toxicity of 5-fluorouracil should be controlled by dose adjustments and supportive measures. These supportive measures include haematopoietic Colony Stimulation Factors (CSF) for prevention of myelosuppression and antibacterials for febrile neutropenia, oral cooling with ice-chips for alleviation of oral mucositis, loperamide and rehydration for treatment of diarrhea, and metoclopramide for nausea or emesis.(chapter 2) Alternatively, in several studies risk factors with predictive value for 5-fluorouracil toxicity have been identified, e.g. age, gender, performance status, genetic polymorphism regarding thymidylate synthetase and dihydropyrimidine dehydrogenase (DPD), chronopharmacology, that warrant future research in order to control toxicity.(chapter 1)

In chapter 4, plasma and urinary pharmacokinetics of oxaliplatin in 33 colorectal cancer patients are described. Pharmacokinetics of oxaliplatin were determined on the basis of platinum (Pt)-levels in plasma-ultrafiltrate. A population pharmacokinetic model for platinum, as a reflection of oxaliplatin pharmacokinetics, was developed. This model may be used to investigate the predictive value of pharmacokinetics for the toxicity of oxaliplatin. The dose-limiting toxicity of oxaliplatin is a cumulative neuropathy, that usually develops after several treatments courses. When a relationship between pharmacokinetics and toxicity of oxaliplatin is assessed, the model can be used for prediction and, subsequently, prevention of neuropathy in individual patients.

Moreover, the relationship between the amount of Pt in 24h urine and in fractionated urine collection periods was established. The high correlation coefficients found indicate that fractionated urine samples in the first 8 hours and the first 10 hours may replace more time consuming 24h urine collection in order to determine individual urinary pharmacokinetics.

As described in chapter 2, drug interactions may influence efficacy and toxicity of cytotoxic treatment significantly, that is caused in part by the low therapeutic index, i.e. ratio of efficacy profits and toxicity detriment, of cytotoxic drugs. The number of possible drug-interactions with cytotoxic drugs has been growing over the years, along with an increase of polypharmacy, especially in the elderly population. In general, cytotoxic drug are administered in an outpatient setting, after preparation and delivery by the hospital pharmacy department, while co-medication of non-cytotoxic agents are usually received from the community pharmacy. This may lead to incomplete medication surveillance. Therefore, a study was conducted to potential drug interactions with 5- fluorouracil (chapter 5), and with irinotecan and oxaliplatin (chapter 6), respectively. Literature was examined for interactions with 5-fluorouracil, and with irinotecan and oxaliplatin. These interactions were classified for documentation evidence and severity level by a panel of medical oncologists and pharmacists. In addition, the clinical significance was determined on a 5 level-scale. In literature, 17 interactions with 5-fluorouracil were found, of which 11 were clinically significant.(chapter 5) Subsequently, all co-medication of 122 colorectal cancer patients that were treated with 5-fluorouracil/folinic acid was examined for interactions with 5-fluorouracil. In addition, toxicity of 5-fluorouracil/folinic acid in these patients was determined according to the NCI-CTCriteria.

Analysis of the co-medication revealed possible clinically significant interactions in 4 patients, that used hydrochlorothiazide (2 patients) or folic acid (2 patients). The occurrence of the interaction between 5-fluorouracil and folic acid may increase in future years, because of the foreseen growing use of folic acid for treatment of

hyperhomocysteinemiae for prevention of cardiovascular events. However, since the dosage of folinic acid that is used for this indication is relatively low, the clinical significance of this interaction is limited.

Toxicity percentages of 5-fluorouracil/folinic acid in this patient group matched with percentages from clinical trials found in literature. Consequently, these results confirm that treatment of colorectal cancer with the combination of 5-fluorouracil/folinic acid is associated with substantial toxicity.

Analogously to the former study, co-medication of 98 patients, that were treated with irinotecan (75 patients) and/or oxaliplatin (52 patients), was evaluated for the occurrence of clinically significant interactions.(chapter 6) Among the interactions, selected from literature, the expert panel identified 11 clinically significant interactions with irinotecan and 1 with oxaliplatin. Of these, dexamethasone (45 patients), loperamide (64 patients), and phenytoin (1 patient) were found as co-medication in irinotecan-treated patients. Assuming dexamethasone and loperamide being applied deliberately for treatment of nausea and vomiting, and diarrhea, respectively, only one patient had been exposed to a significant interaction, i.e. with phenytoin. Although the occurrence of clinically significant interactions in both studies, regarding 5-fluorouracil, and irinotecan and oxaliplatin, was low, the agents with significant interacting potential, as indicated by the expert panels, should be added to interactions-databases for medication-surveillance.

In two phase III trials, capecitabine, a new oral prodrug of 5-fluorouracil, was at least as effective as 5-fluorouracil plus folinic acid in the treatment of metastatic colorectal cancer. In addition, capecitabine showed a more favourable toxicity profile, as well as the convenience of oral administration at home. In chapter 7, the results are presented of a cost-benefit analysis to assess the pharmaco-economic profile of capecitabine compared with 5-fluorouracil/folinic acid, given according to the Mayo regimen, for colorectal cancer patients treated in the Netherlands. Based on data from 65 patients, this cost-benefit analysis revealed that the higher acquisition costs of capecitabine were more than compensated for by the reduced costs for travel expenses, hospital care (limited number of outpatient visits vs inpatient treatment for 5-fluorouracil/folinic acid), and toxicity management. Baseline savings were estimated at € 1610 for palliative treatment and € 934 for adjuvant treatment, suggesting that treatment of colorectal cancer with oral capecitabine is cost-saving in the Netherlands compared with 5-fluorouracil plus folinic acid administered according to the Mayo regimen.

Recommendations

In the present thesis, various aspects of chemotherapy in the treatment of colorectal cancer are considered that are more or less appropriate for interventions by clinical pharmacists. For instance, risk factors for toxicity, that are dependent of the cytotoxic agent used, are potential starting-points for toxicity control. Currently, the clinical pharmacist may be involved in guideline discussions to choose the dose-regimen of 5-fluorouracil or irinotecan with the most suitable toxicity profile for individual patients, next to calculating the dose from the estimated body surface area. In addition, dose adaptation based on performance status and age is a target for toxicity control of these two agents. In future, along with the increasing interest in pharmacogenetics, genetic polymorphism of the enzymes dihydropyridine dehydrogenase (DPD) and uridine 5'-diphosphate-glucuronyltransferase-1A1 (UDPGT-1A1) may lead to screening of patients for altered pharmacokinetics of 5-fluorouracil and irinotecan, respectively, in order to prevent significant toxicity in patients with enzyme-polymorphism.[6,7]

The supportive measures for prevention or alleviation of toxicity symptoms that are presented can be used for development of treatment protocols as well as individual control of treatment-related toxicity by the clinical pharmacist.

Nowadays, therapeutic drug monitoring of cytotoxic agents is mainly applied in investigational settings. In clinical practice, no cytotoxic agent used in the treatment of colorectal cancer is routinely monitored based on plasma-concentrations. Our results regarding 5-fluorouracil do not oppose this practice, whereas the pharmacokinetic model that has been established for oxaliplatin needs further investigation with regard to toxicity control. However, since therapeutic drug monitoring has been shown to be effective in controlling the toxicity of 5-fluorouracil in some studies, this concept still offers potential benefits that have to be elucidated. Several drug-interactions with 5-fluorouracil and irinotecan have been shown to be clinically significant, and are therefore erroneously disregarded in medication-surveillance in (Dutch) clinical practice. The clinical pharmacist should be on the alert for these interacting agents, as well as yet non-identified agents that may interact significantly with other cytotoxic drugs, and intervene if necessary.

Pharmaco-economics is becoming increasingly important in assessing the benefits of new (cytotoxic) drugs. In fact, as from 2005, manufacturers are required to deliver a pharmaco-economic evaluation in order to obtain a registration licence in the Netherlands.[8] In this thesis, capecitabine has been proven to be cost-saving in comparison with 5-fluorouracil/folinic acid in the treatment of Dutch colorectal cancer patients. As for other new agents, the clinical pharmacist can make an essential contribution to the performance and the interpretation of this type of investigation, both on a national scale and in a local setting. Accordingly, the Netherlands

Association of Hospital Pharmacists should anticipate to this development by offering education and by supporting and coordinating studies in this area.

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