Acta Oncologica, 2007; 46: 735–740

informa
healthcare

ORIGINAL ARTICLE

Treatment modifications of antineoplastic drugs in an oncology day-care unit

EVA R. BREMBERG[1], SAMUEL ROTSTEIN[2] & STAFFAN EKSBORG[1,3]

[1]*Karolinska Pharmacy, Karolinska University Hospital, Danderyd Hospital, Stockholm, Sweden,* [2]*Department of Oncology, Karolinska University Hospital, Danderyd Hospital, Stockholm, Sweden and* [3]*Department of Woman and Child Health, Childhood Cancer Research Unit, Karolinska Institutet, Stockholm, Sweden*

Abstract

The frequency of and reasons for treatment modifications related to prescriptions of antineoplastic drugs and to what extent the modifications are performed in accordance with the local treatment protocol were studied at an oncology day-care unit. Ninety-three patients were treated with antineoplastic drugs at the unit during the study period. Their diagnosis included mainly breast- and gastrointestinal tumours. Thirty-eight treatment modifications in relation to the treatment protocol were observed in 31 of 93 patients (33%). Twenty-five of 31 patients were treated with palliative intention (81%). Two treatment modifications of 38 (5%) were in accordance and 21 modifications (55%) were not in accordance with the local treatment protocol. It was not possible to verify whether the remaining 15 modifications (39%) were according to the protocol. Adverse effects were the most common reason specified in the medical file for treatment modification (8 patients; 26%). The reasons for treatment modification were only documented in the medical file for 11 of 31 patients (35%) and only present on the prescription card delivered to the local pharmacy for one of 31 patients (3%). Drug interactions were not considered according to the medical files for any of the 93 patients who were treated at the unit during the study days, and accordingly, no treatment modifications had been performed due to drug interactions. Liver and/or renal function tests were missing in the medical file for four patients treated with drugs for which these tests are crucial. More emphasis should be put on identifying clinically relevant drug interactions between antineoplastic drugs and the patient's regular drugs and also on specifying the reason for modifications in the medical file and on the prescription cards delivered to the local pharmacy. Increased quality assurance of the local treatment protocols is warranted.

In the routine care of patients with cancer diseases treatment with antineoplastic drugs is mostly given according to pre-specified protocols. In particular in the adjuvant setting, it is important to maintain the scheduled doses and intervals, in particular in the adjuvant setting as the clinical outcome normally correlates to the dose intensity. However, in clinical practice treatment modifications are often needed due to various reasons.

In many countries, pharmacists are checking prescriptions of antineoplastic drugs at the day-care units or in the wards. The medical files including laboratory data are available for the pharmacists, giving the possibility to interpret reasons for treatment modifications [1–5].

In Sweden, the check of antineoplastic drug prescriptions is performed by the pharmacist in the antineoplastic drug unit of the local pharmacy. The responsibility of the pharmacist is, among other things, to estimate if the prescribed dose is reasonable. However, it is not possible for the Swedish pharmacists to verify the appropriateness of treatment modifications due to lack of access to medical files and laboratory data.

The importance of the contribution of the pharmacist to the multidisciplinary team in an oncology ward is well documented. In a recent study, 114 drug-related problems in 58 patients were detected by a pharmacist, albeit prescriptions of antineoplastic drugs were not studied [6].

It is not known how frequent treatment modifications occur in antineoplastic drug prescriptions, neither what are the most common reasons for modifications nor to what extent the modifications

Correspondence: Eva Rämme Bremberg, Pfizer AB, SE-191 90 Sollentuna, Sweden. Tel: +46 8 550 527 90. Fax: +46 8 550 520 10. E-mail: eva.bremberg@pfizer.com

(Received 15 August 2006; accepted 26 March 2007)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860701373561

are performed in accordance with the current treatment protocols.

The aims of this project were to, in the routine care at a day-care unit, study the frequency of and reasons for treatment modifications related to prescriptions of antineoplastic drugs and to what extent the modifications were performed in accordance with the local treatment protocol.

Material and methods

The project was performed in the routine care in the oncology day-care unit at Danderyd Hospital, Stockholm, Sweden, during 2 weeks in early spring 2006. Ninety-three patients were treated with antineoplastic drugs at the unit during the study period. Their diagnosis included various types of solid tumours, mainly breast- and gastrointestinal tumours. Twenty-eight of the patients were treated with curative intention (30%), Table I. Seventy-five patients were treated once and 18 patients were treated twice, i.e. totally 111 treatments were given during the study period. Another three patients were booked for treatment that was postponed due to too low peripheral blood cell counts. None of the 93 patients were participating in clinical trials.

Treatment regimens

Twenty-three different treatment regimens were used. FEC75, including 5-fluorouracil (600 mg/m^2), epirubicin (75 mg/m^2) and cyclophosphamide (600 mg/m^2) was the most common regimen (13 patients). The second most common regimens were Herceptin 3 V (trastuzumab every 3 weeks, 10 patients), Campto-Flv (irinotecan, 5-fluorouracil and calcium-folinate, 10 patients) and Gemzar (gemcitabin, 10 patients).

Table I. Patient and treatment characteristics.

	Number of patients	Age; median (range)	Curative intention
Sex			
Female	68 (73%)	62 (26–92)	
Male	25 (27%)	67 (43–79)	
Tumour type			
Breast	51 (54%)		20 (39%)
Colon	21 (22%)		7 (33%)
Rectum	7 (8%)		0 (0%)
Pancreas	7 (8%)		0 (0%)
Other gastrointestinal tumour	7 (8%)		1 (14%)

Routine for ordering of antineoplastic drugs from the pharmacy

For each drug regimen there is a specific prescription card. The local treatment protocols are presented on the back side of the prescription cards. The protocols contain detailed information about dose (mostly mg/m^2), administration time, treatment intervals and also the order in which the antineoplastic drugs and supportive drug therapy should be given. The protocols also include some information about when and how dose modifications should be undertaken, e.g. due to low blood cell counts, impaired liver or renal function, neurological symptoms.

The patient's name, date of birth, diagnosis, height and weight as well as the blood cell counts (generally measured the day before treatment) are filled in by the nurses on the prescription card specific to the actual antineoplastic drug regimen.

Individual therapy decisions are taken on weekly therapy conferences with the physicians at the unit participating. All physicians are familiar with all the tumour types treated at the unit. Only senior physicians are allowed to sign prescription cards for antineoplastic drugs.

Body surface area (BSA) is estimated from the height and weight of the patient by the responsible physician. The physician calculates the dose based on the BSA. A special doctor is on a daily basis scheduled to sign prescriptions for all patients at the unit at a specific time during the day before ordering of the antineoplastic drugs from the pharmacy. It is this doctor's duty to adjust the dose if necessary. The physician fills in the final dose on the prescription cards and finally signs them in the presence of the nurse. In case of dose adjustment the percentage of the protocol dose is presented on the prescription card. The prescription is finally delivered to the antineoplastic drug preparation unit of the local pharmacy the day before the patient comes to the unit. Protocol adjustments can thus occasionally be performed based on the communication between the patient and the nurse as patients are not necessarily seen by their physician before each antineoplastic cycle.

Performance of the study

Copies of the booking lists and the prescription cards were made at the unit by one of the authors (ERB, a clinical pharmacist) before they were delivered to the antineoplastic drug preparation unit of the local pharmacy in order not to disturb the normal routine at the ward. The following parameters for antineo-

plastic drug prescriptions were checked in all patients who were treated at the unit during the study period:

1. The frequency of treatment modifications in relation to the local treatment protocol;
2. If the treatment modifications had been performed in accordance with the local treatment protocol;
3. The reasons for the treatment modifications;
4. If the reasons for treatment modifications were presented on the prescription cards;
5. If clinically relevant interactions had been considered;
6. If the maximum cumulative dose had been considered for anthracyclines;
7. If other factors indicating reasons for the prescribed treatment to be modified had been taken into account.

Ethical considerations

The study was performed as a quality control project without affecting the routine care at the unit. Supplementary data from the medical files were collected by hand writing on a separate sheet of paper. The copies of the antineoplastic drug prescriptions and the sheets with supplementary data from the medical files were unidentified and given a study specific number. Only unidentified data were saved and processed. Data are only presented on an aggregated level.

Results

Treatment modifications

Thirty-eight treatment modifications in relation to the local treatment protocol were observed in 31 of 93 patients (33%, 95% CI: 23.9 to 43.8%) who were treated at the unit, Figure 1. Twenty-five patients of 31 were treated with palliative intention (81%). In addition, there were 15 patients with a temporary treatment modification, e.g. extended interval due to surgery or other diseases.

The interval had been changed in 12 of 31 patients. In eight patients, the scheduled interval between treatments had been extended by 1 week (seven patients) and 2 weeks (one patient). In four patients the time span since the previous treatment had been extended occasionally.

The dose had been adjusted in 22 of 31 patients. Decreased dose, in 18 patients (82%, 95% CI: 59.7 to 94.8%), was the most common dose adjustment. The dose was increased in two patients, (9%, 95% CI: 1.1 to 29.2%). In one patient, vinorelbine had been prescribed as oral instead of intravenous treatment as stated in the protocol on the back side of the same prescription card. One patient had got starting dose of trastuzumab after a treatment break but no information about how to restart treatment could be found in the treatment protocol.

Accordance to the local treatment protocol

Two of 38 treatment modifications (5%) were in accordance and 21 modifications (55%) were not

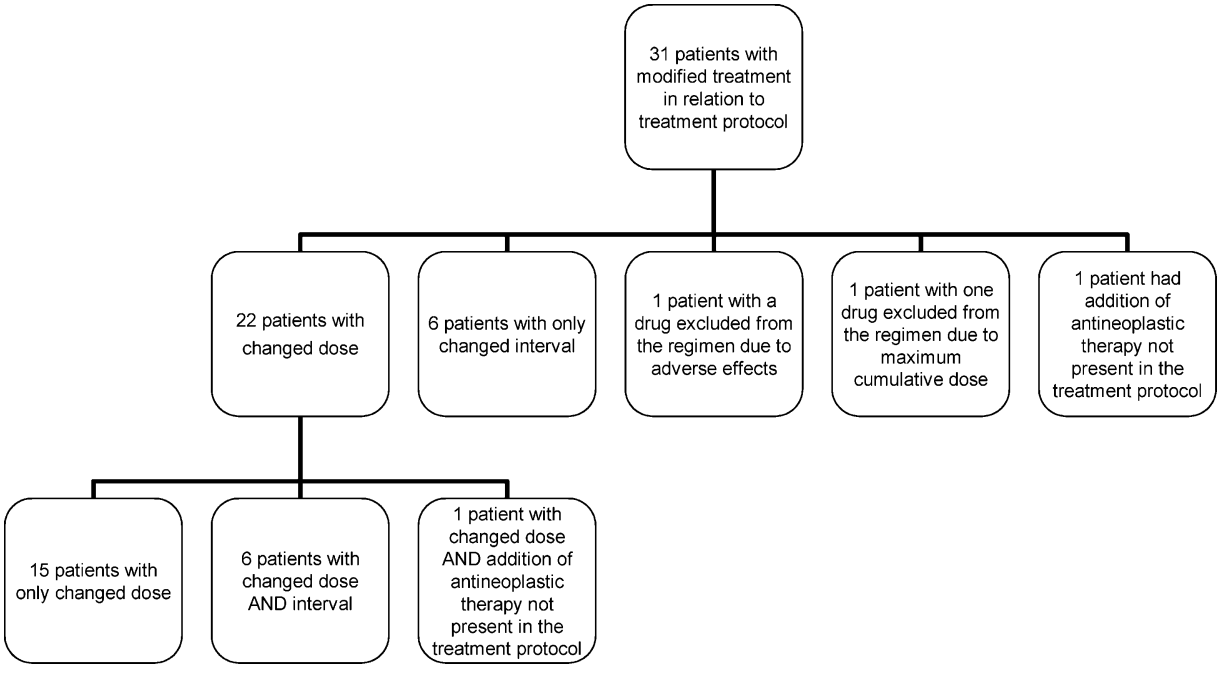

Figure 1. Patients with treatment modifications in relation to the treatment protocol who were treated at the unit during the study period.

in accordance with the local treatment protocol, Figure 2. It was not possible to verify whether 15 of the modifications (39%, 95% CI: 24.1 to 56.7%) were according to the protocol.

Reasons for modification

Adverse effects, including insufficient peripheral blood cell counts (three patients), neurological symptoms (two patients), vomiting/diarrhoea (two patients) and indistinct swelling in the body (one patient), were the most common reason specified in the medical file for treatment modification (8 patients; 26%, 95% CI: 11.9 to 44.6%), and other reasons were specified for three patients, Table II.

The reasons for treatment modification were not documented in the medical file for 20 of 31 patients (65%, 95% CI: 45.4 to 80.8%). Seventeen of these patients were treated with palliative intention (85%). Thirteen patients of 20 had gastrointestinal cancer and seven patients had breast cancer.

Reason for modification available on prescription card

In one of the 31 patients with a modification of the prescription cards delivered to the local pharmacy (3%, 95% CI: 0.1 to 16.7%), the reasons for the modification were present and in the remaining 30 the reasons were not given.

Clinically relevant drug interactions

Drug interactions had not been considered according to the medical files for any of the 93 patients who were treated at the unit during the study period and accordingly, no treatment modifications had been performed due to drug interactions.

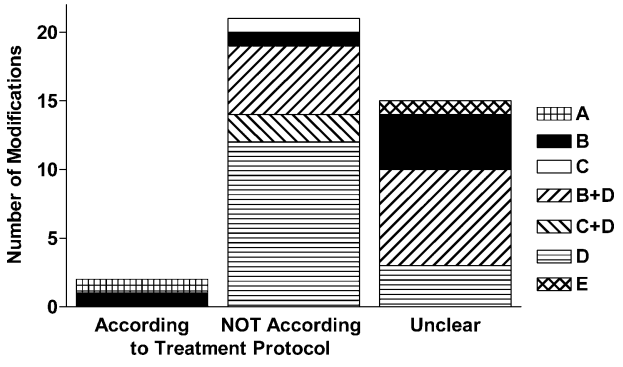

Figure 2. Treatment modifications – accordance to the local treatment protocol. A. Excluded drug as cumulative maximum dose had been reached; B. Change in interval only; C. Addition of antineoplastic drug not present in the treatment protocol; B+D. Change in dose AND change in interval; C+D. Change in dose AND addition of antineoplastic drug not present in the treatment protocol; D. Change in dose only; E. Excluded drug due to adverse effects.

Table II. Reasons specified in the medical file for treatment modification.

Reason for modification	Number of patients
Adverse effect	8 (26%)
Unspecified reason	20 (65%)
Cardiac function	1 (3%)
Extended time span due to fracture in the arm	1 (3%)
Maximum cumulative dose reached	1 (3%)

Maximum cumulative dose for anthracyclines

Twenty-one patients had a regimen including an anthracycline. For one of these patients the maximum cumulative dose had been considered, 17 patients had not yet reached the maximum cumulative dose and three patients were about to get their first treatment.

Other factors to be taken into account

Both liver- and renal function tests were missing for one patient with 5-FU and renal function tests were also missing for one patient with capecitabine. Liver function tests were also not available in the medical file for one patient with liposomal doxorubicin and one patient with docetaxel.

For one patient with an actual body surface area (BSA) of 2.4 m^2, the doses of irinotecan and cetuximab were based on a BSA of 2.0 m^2.

There was no guidance in the local treatment protocols when to discontinue treatment in the palliative situations.

Discussion

Thirty-one of 93 patients who were treated at the unit during the study period had at least one treatment modification in relation to the local treatment protocol. It was observed that only two modifications of 38 in these 31 patients were in accordance with the local treatment protocol.

In a study of dose-dense adjuvant chemotherapy in early breast cancer patients treated with fluorouracil, epirubicin and cyclophosphamide (FEC), the dose intensity did not affect hazard of death or recurrence rate [7]. Therefore, the most common treatment modification observed in the present study, i.e. change in dose and/or dose interval, Figure 2, might not be considered as a major problem in the entire population, but might be of concern for the individual patients.

The reason for the modification was documented in the medical file only for 11 of 31 (35%) of the patients, and also, the reason was present on only one of 31 (3%) of the prescription cards delivered to the local pharmacy. It has to be noticed that there is no specific place on the prescription cards that is intended for information about treatment modifications. These facts make it difficult for the local pharmacist to check whether the modifications have been performed in accordance with the local treatment protocol.

Interviews with nurses and doctors at the unit revealed that information about the patient status given to the doctors by the nurses often result in treatment modifications and also that such modifications are not always documented.

The decision of treatment to be given is based on the objective laboratory data and on the subjective information given by the nurses about the patient's general condition. If, for example, the previous prescription was modified and the patient is well according to the nurse, these criteria might be enough to maintain a modification, especially in the palliative setting, even though the criteria are not specified in the local treatment protocol.

Several reasons might explain the lack of documentation. It is unclear who (the doctor or the nurse) is responsible for this documentation. It might therefore be useful to clarify the responsibilities in this respect. The nurses however sometimes need to consult a specific doctor during the day before ordering the antineoplastic drugs from the pharmacy. Such last minute changes might not always be documented. Both nurses and doctors informed us that the patient's general condition is a common reason for dose modifications, mainly resulting in decreased doses. Most of the patients with treatment modifications compared to the local treatment protocol had a palliative intention of the treatment (25 of 31 patients; 81%). In the curative setting there was a stricter adherence to the local treatment protocols. Our results indicate that there are other factors influencing the decision about the treatment besides those presented in the local treatment protocol.

Drug interactions had not been considered according to the medical files for any of the 93 patients who were treated at the unit during the study period and consequently no treatment modifications had been performed due to drug interactions. Several of the antineoplastic drugs used at the unit have potential clinically relevant interactions with commonly used drugs. No information about drug interactions that are important to consider were given in the local treatment protocols.

Thirteen patients were treated with regimens including irinotecan. According to the Summary of Product Characteristics (SmPC) for irinotecan, concurrent use with St. John's Worth (Hypericum perforatum, HP) is contraindicated as HP lowers the plasma concentration of the active metabolite of irinotecan. No information was found in the medical files about if the patients had been asked about their use of HP. According to our experience many patients with cancer disease are using natural remedies, which imply potential risks for interactions with antineoplastic drugs. However, there is a lack of knowledge concerning drug interactions for many natural remedies.

One patient with a treatment regimen including 5-fluorouracil (5-FU) had also got a prescription of metronidazole. This combination means an increased risk for adverse effects due to reduced clearance of 5-FU.

In a pilot study with a pharmacist in an oncology ward in Sweden 37 potential drug interactions were identified (without assessment of the clinical relevance) among 100 oncology patients (pers. comm. M. Bokinge, Linköping University Hospital, Sweden). In another Swedish study in an oncology ward, 14 drug interactions were identified and assessed as clinically relevant by the pharmacist in 58 patients [6].

These findings suggest that (1) information about clinically relevant interactions should be included in the local treatment protocols and (2) more emphasis could be put on identifying potential clinically relevant drug interactions between antineoplastic drugs and the patient's regular drugs when collecting the drug history and prescribing the chemotherapy. Pharmacists can play an important role in collecting drug history and identification of drug interactions as stated by the examples above.

Other factors identified, indicating possible reasons for the prescribed treatment to be modified were liver and renal function, body surface area and quality of life.

Liver and/or renal function tests were missing in the medical file for four patients treated with drugs for which these tests are crucial. For docetaxel, liver function tests should be taken before treatment start and also before to each cycle of treatment according to the SmPC. This information was missing in the local treatment protocol.

For one patient with an actual body surface area (BSA) of 2.4 m^2, the doses of irinotecan and cetuximab were based on a BSA of 2.0 m^2. Albeit only limited data on disposition of antineoplastic drugs in obese patients is available, there is data indicating that routine dose reduction for obese

patients based on limitation of the BSA to 2 m^2 might decrease the treatment efficacy [8].

One patient with palliative trastuzumab treatment experienced that the treatment gave a bad quality of life according to the medical file. There was no guidance in the local treatment protocol about when to discontinue treatment in the palliative situation. Information about discontinuation of treatment was in fact lacking in most of the commonly used local treatment protocols including protocols for gastro-intestinal cancer. Even though rules are given in therapy conferences and care programmes, it seems like these decisions are not transferred into the local treatment protocols used for the final decision of treatment discontinuation at the out-patient unit.

Conclusions

More emphasis could be put on identifying clinically relevant drug interactions between antineoplastic drugs and the patient's regular drugs and also on specifying the reason for modifications in the medical file and on the prescription cards delivered to the local pharmacy. Increased quality assurance of the local treatment protocols with respect to inclusion of relevant information from the Summary of Product Characteristics (SmPC) might be needed.

Acknowledgements

The authors wish to thank the staff at the unit for pleasant co-operation and in particular the nurses Maria Fahlberg and Mai Näsström for assistance during the project.

References

[1] Waddell JA, Solimando DA Jr, Strickland WR, Smith BD, Wray MK. Pharmacy staff interventions in a medical center hematology-oncology service. J Am Pharm Assoc (Wash) 1998;38:451–6.

[2] Pon D. Service plans and clinical interventions targeted by the oncology pharmacist. Pharm Pract Manag Q 1996;16:18–30.

[3] Wong WM, Ignoffo RF. If there are expert systems and dose checks, why do we still need the clinical pharmacist? Pharm Pract Manag Q 1996;16:50–8.

[4] Caselnova DA 3rd, Dzierba SH, O'Neill MS, Dillon KR, Farley PC. Implementing clinical pharmacy services in an outpatient oncology clinic. Am J Hosp Pharm 1985;42: 1348–52.

[5] Honda DH. Role of the clinical pharmacist in oncology care. Front Radiat Ther Oncol 1981;15:157–61.

[6] Bremberg ER, Hising C, Nylén U, Ehrsson H, Eksborg S. An evaluation of pharmacist contribution to an oncology ward in a Swedish hospital. J Oncol Pharm Practice 2006;12:75–81.

[7] Venturini M, Del Mastro L, Aitini E, et al. Dose-dense adjuvant chemotherapy in early breast cancer patients: Results from a randomized trial. J Natl Cancer Inst 2005;97:1712–4.

[8] Navarro WH. Impact of obesity in the setting of high-dose chemotherapy. Bone Marrow Transplant 2003;31:961–6.