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An evaluation of adverse reactions to induction treatment in AC and AT schemes of locally advanced breast cancer

Edyta Szałek[1], Agnieszka Kamińska[1], Maria Litwiniuk[2], Edmund Grześkowiak[1], Karol Połom[3]

[1] The Department and Unit of Clinical Pharmacy and Biopharmacy, University of Medical Sciences, Poznań
[2] The Oncological Clinic, University of Medical Sciences, Poznań
[3] Wielkopolska Cancer Centre, Poznań, 1st Clinic of Surgical Oncology

Summary

Introduction. Breast cancer is the most frequent malignant cancer found in women. In 2003 in Poland the number of registered cases was 11,733. The most common treatment method is surgery. Some patients need to have induction chemotherapy to reduce the mass of the tumour [1]. ***Aim***. The aim of this paper was to evaluate the frequency of occurrence and intensity of adverse reactions to two neoadjuvant therapy schemes: AC (with cyclophosphamide and doxorubicin) and AT (with doxorubicin and docetaxel). ***Material and methods.*** A retrospective analysis of adverse reactions was made on 25 patients with breast cancer (9 patients aged 31-56 treated with the AT scheme and 16 patients aged 30-65 with the AC scheme) treated at the Oncological Clinic, University of Medical Sciences, Poznań from 2004 to 2006. The drugs were administered intravenously in the following doses: docetaxel 75 mg/m^2 (120-140 mg), doxorubicin 60 mg/m^2 (80-120 mg) in the AC scheme and 50 mg/m^2 in the AT scheme, cyclophosphamide 600 mg/m^2 (900-1200 mg). The treatment cycles were repeated every 21 days. ***Results.*** The most frequently observed adverse reactions were: alopecia (100%), nausea (AC - 59%, AT - 37%), vomiting (AC - 29%, AT - 12%), menstruation disorders (AC - 23%, AT - 37%), stomatitis (AC - 29%, AT - 37%), fever (AC -23%, AT - 25%), no appetite (AC - 23%, AT - 12%), leucopoenia (AT - 25%). In the analysed group the following unexpected adverse reactions were observed: metallic aftertaste in the mouth (AC - 23%), hypersensitivity to light (AC - 23%), increased thirst (AC - 23%), elbow and knee itching (AT - 12%), increased perspiration (AC - 6%). ***Discussion.*** In the analysed group of patients the treatment of malignant breast cancer with the AT scheme resulted in more adverse reactions than in the case of the AC scheme. During the AC scheme therapy a large number of unexpected adverse reactions were observed. *(Farm Współ 2009; 2: 3-9)*

Keywords: adverse reactions, breast cancer, AC and AT scheme

Introduction

The application of drugs involves the possibility of occurrence of adverse reactions, which may endanger the patient's health and life. An adverse drug reaction (ADR) is a harmful and unintended reaction of a therapeutic substance, which occurs during the application of doses recommended to people for the purpose of prophylaxis, diagnosis, treatment of diseases or modification of physiological functions [2]. At present there is a wide range of ADR categorisations. The most common categorisation includes reactions of the following types: A (dose-related; augmented), B (non-dose-related; bizarre), C (dose-related and time-related; chronic), D (time-related; delayed), E (withdrawal; end of use), F (failure of therapy; failure [3]. As a number of examinations show, adverse drug reactions have a direct influence on prolonged hospitalisation time, increased death rate and higher costs of hospitalisation [4,5]. There are a number of ways of monitoring adverse drug reactions [6]. One of the simpler methods, which lowers the risk of occurrence of drug-induced reactions, is to interview the patient about the risk factors and to constantly monitor the

patients who are particularly endangered to adverse reactions during the pharmacotherapy. Such an interview can be made by qualified personnel (e.g. physicians, clinical pharmacists, nurses). Retrospective analyses of patient cards may lead to errors, because not all of the drugs dispensed to the patient are taken into consideration. What turns out to be useful is computer programs, which facilitate the collection of necessary data and relating it with effective ADR monitoring [6]. One of such programs applied by Food and Drug Administration (FDA) in the USA was a Bayesian data mining system called Multi-item Gamma Poisson Shrinker (MGPS) to enhance the FDA's ability to monitor the safety of drugs [7].

Chemotherapy is a method of very aggressive treatment. Therefore, it is very important to prevent drug-induced complications and control the symptoms of adverse drug reactions. Among oncological patients women with breast cancer deserve special attention, because this type of cancer is the most frequent in women. It is estimated that every year in Poland about 30 out of 100,000 women will develop breast cancer. At the moment of diagnosis in many of the women the disease is locally advanced. Most frequently this is a non-operable tumour or 'hardly operable'. The patient undergoes initial chemotherapy (induction), whose aim is to reduce the size of the tumour and to enable radical surgical treatment. Another advantage resulting from pre-operational chemotherapy is the possibility to destroy distant micrometastases [1,8,9]. A patient with breast cancer has lost such an important value as health, found herself in an unknown and unexpected situation which is accompanied by the stress connected with the waiting for an unpleasant experience related with the treatment, which may be accompanied by numerous adverse reactions to chemotherapy. Therefore, what seems to be so important is to constantly monitor the safety of the therapy with cytostatics.

During induction chemotherapy the treatment of patients is very often based on polypragmasy. Apart from the cytostatics administered at regular time intervals patients receive the drugs applied in concomitant diseases and undergo a therapy reducing the expected adverse reactions to chemotherapy. In consequence of such a complex therapy adverse drug reactions are intensified, which may be mistaken for the symptoms of the primary disease. The phenomenon of polypragmasy and primary systemic treatment are accompanied by the difficulty of interpretation of adverse reactions.

Table 1. Characterisation of patients

	AC Scheme	AT Scheme
Number of patients	16	9
Age [years] (median)	30 – 65 (49)	31 – 56 (44)
Concomitant diseases	Hypertension - 5 Aspirin allergy – 1 Hashimoto's disease – 1 Depression – 1 Diabetes – 1 Hypothyroidism - 2	Diabetes - 1
Hormonal treatment	Contraception – 3 (1- cyproteron acetate 2mg, - ethinylestradiol 0.035mg; 2 - desogestrel 0.15mg, - ethinylestradiol 0.03mg; 3 - desogestrel 0.15mg, - ethinylestradiol 0.02mg). hormone substitution therapy - 2 (estradiol 1.25mg)	Hormone substitution therapy - 1 (estradiol 1.25mg)
Currently received drugs	levothyroxine 50µg (2) cetirizine dihydrochloride enalapril maleate 10mg (4), bisoprolol fumarate 5mg, gliclazide 30mg, imipramine hydrochloride 5mg;	Insulin preparation
Occurrence of neoplastic diseases in relatives	Neo (+) - 5 Neo (-) - 11	Neo (+) - 6 Neo (-) - 3

Table 2. A comparison of adverse reactions to the induction treatment with AC and AT schemes

Adverse reaction	AC scheme		AT scheme	
	Number of patients	[%]	Number of patients	[%]
Alopecia	16	100	9	100
Nausea	13	81	6	67
Vomiting	7	44	3	33
Stomatitis	6	37	2	22
Chest pains	1	6	1	11
Weakness	2	12	2	22
No appetite	4	25	1	11
Conjunctival burning sensation	1	6	0	0
Increased body mass	4	25	0	0
Reduced body mass	1	6	2	22
Dyspnoea	2	12	0	0
Fever	5	31	2	22
Increased perspiration	2	12	2	22
Stomach-ache	1	6	0	0
Urticaria	1	6	0	0
Metallic aftertaste in mouth	3	19	1	11
Skin exfoliation	3	19	2	22
Constipation	4	25	0	0
Diarrhoea	3	19	3	33
Increased thirst	3	19	0	0
Fatigue	1	6	1	11
Hypersensitivity to light	4	25	0	0
Menstruation disorders	4	25	3	33
Elbow and knee itching	2	12	0	0
Hypogastric pains	0	0	1	11
Limb pains	1	6	2	22
Headache	0	0	0	0
Muscle pains	2	12	1	11
Superficial thrombophlebitis	0	0	0	0
Phlebitis	2	12	1	11
Onycholysis	0	0	1	11
Lower limbs swelling	0	0	1	11
Leucopoenia	3	19	5	55
Heartburn	0	0	1	11

Table 3. A comparison of unexpected adverse reactions to the induction treatment with AC and AT schemes

Unexpected reaction	AC scheme		AT scheme	
	Number of patients	[%]	Number of patients	[%]
Increased thirst	3	19	0	0
Increased perspiration	2	12	2	22
Hypersensitivity to light	4	25	0	0
Metallic aftertaste in mouth	3	19	1	11
Elbow and knee itching	2	12	0	0

This results from the non-specific character of adverse reactions, e.g. nausea, vomiting, diarrhoea.

The aim of this paper was to analyse the reported suspected occurrences of adverse reactions to AC and AT scheme drugs of the neoadjuvant treatment of locally advanced breast cancer registered in the Department of Chemotherapy, Oncological Clinic, 1st Independent Public Clinical Hospital from 2004 to 2006 as part of the internal monitoring system of adverse drug reactions.

Patients and methods

The paper presents an evaluation of the frequency and intensity of the observed adverse reactions to two most frequently applied schemes of neoadjuvant treatment of breast cancer, i.e. AC (doxorubicin, cyclophosphamide) and AT (doxorubicin, docetaxel). For this purpose the patients treated at the Department of Chemotherapy were monitored from June 2004 to May 2006. The data obtained in 2004 comes from a retrospective analysis of patient cards. The data from 2005 and 2006 came from an interview with patients with breast cancer, who were currently undergoing a neoadjuvant therapy. A questionnaire was prepared for this purpose, which was filled in by a physician cooperating with a pharmacist.

An analysis of adverse reactions was made in 25 patients due to the locally advanced breast cancer. Table 1 presents a detailed characterisation of the patients. The drugs were administered intravenously in the following doses: docetaxel 75 mg/m^2 (120-140 mg), doxorubicin 60 mg/m^2 (80-120 mg) in the AC scheme and 50 mg/m^2 in the AT scheme, cyclophosphamide 600 mg/m^2 (900-1200 mg). The treatment cycles were repeated every 21 days.

Results

As a result of the analysis of reports of suspected occurrences of adverse reactions to cytostatics in the Department of Chemotherapy, Oncological Clinic, University of Medical Sciences, Poznań the following ADR symptoms of induction breast cancer treatment with AC and AT schemes were observed and presented in Table 2. Table 3 presents a comparison of unexpected adverse reactions to the treatment.

Discussion

Mammary gland cancer is one of more than 200 different types of neoplasms characterised by: location, degree of progression, growth dynamics, microscopic structure, organ and systemic physiopathology, immunological and biochemical characteristics [10]. Depending on the degree of clinical progression, age, hormonal state, tumour growth speed, general condition and concomitant diseases the following methods of breast cancer treatment can be distinguished: surgical (SG), radiotherapy (RT), immunotherapy (IT), chemotherapy (CHT) and hormonotherapy (HT). The evolution of treatment strategies was influenced by such factors as: obtaining new, more efficacious chemical and hormonal drugs, improvement in surgical treatment techniques and irradiation.

In breast cancer patients hormonotherapy is applied as a supplementary and palliative treatment both to the patients before the menopause and to those after it. It is tamoxifen that plays an important role in the supplementary treatment. However, in the case of post-menopause patients more and more attention is paid to aromatase inhibitors: anastrozole, letrozole, exemestane [8,11]. The systemic treatment which is applied in generalised breast cancer is by assumption only a palliative procedure. The primary goal is to relieve the ailments related with the disease, improve the quality of life and prolong the survival. In medical practice aromatase inhibitors are applied, e.g. anastrozole and letrozole, as well as antiestrogens, e.g. fulvestrant ('pure' antagonist).

The use of cytostatics in medical practice has three main types of application: neoadjuvant treatment, adjuvant treatment and the treatment of patients with generalised breast cancer. The idea of induction treatment is to lower the degree of clinical progression, reduce the size of the tumour (in order to carry out surgical treatment), destroy distant micrometastases and to minimise the likelihood of early generalisation of the disease [1, 8, 9]. Supplementary chemotherapy is applied after the surgical treatment. It prolongs the period of asymptomatic survival and increases the total survival rate in the patients who underwent the adjuvant treatment in comparison with the ones who did not undergo the treatment after the surgery. Chemotherapy should be applied within 4-6 weeks after the surgery. The treatment of generalised breast cancer is a palliative procedure, because it is an incu-

rable disease. The primary goal is to relieve the ailments caused by metastases, prolong the survival time and improve its quality. The drugs of high clinical activity in the treatment of breast cancer are oncotherapeutic drugs: anthracycline antibiotics, cyclophosphamide, docetaxel, paclitaxel, vinorelbine, capecitabine and trastuzumab – a monoclonal antibody which binds with HER-2 receptor.

For almost three decades multidrug chemotherapy, whose usefulness was based both on theoretical assumptions and practical experience, has been constantly evaluated with respect to the application of drugs without cross resistance and with different toxicity profiles. However, cytostatics belong to the drugs of high affinity with normal cells. Therefore, there are such a high number of adverse reactions caused by these drugs [12].

The aim of this paper was to analyse the reports of suspected occurrences of adverse reactions to cytotoxic drugs: doxorubicin, docetaxel and cyclophosphamide and to compare the adverse reactions to the neoadjuvant breast cancer treatment with the AC and AT schemes. The most frequently described adverse reactions observed after the application of the aforementioned cytostatics are: leucopoenia, neutropenia, alopecia, cardiotoxicity, hypersensitivity reactions, fever, mucosal reaction [12-14].

In consequence of the analysis of the suspected occurrences of adverse reactions in oncological patients of the Department of Chemotherapy, Oncological Clinic in 2004-2005 the following data was obtained. The most frequently observed adverse reactions were (according to WHO - toxicity III and IV): alopecia – 100% (III – complete but reversible loss of hair) and leucopoenia - 11% (IV, treatment with AT scheme), 22% (III, treatment with AT scheme), 6% of the patients (III, treatment with AC scheme). The other adverse reactions were evaluated as toxicity I/II according to the WHO classification. The physiological discomfort which accompanies the treatment with cytostatics and which includes nausea and vomiting was observed in the patients in the AC scheme (81% - nausea, 44% - vomiting) and in the AT scheme (67% - nausea, 33% - vomiting). The reported cases of vomiting were qualified as temporary, which was aided by appropriate premedication in the form of antiemetics. The patients received preparations containing ondansetron. The application of antiemetics may have resulted in an adverse reaction, which was constipation (in 25% - mild; AC). Degree II of mucositis was observed (in the form of erythema, ulceration, the patients were able to take solid food) in 37% (AC) and 22% (AT) of the patients. The mucosal reaction and, as the patients specified it, a metallic aftertaste in the mouth were observed in 19% (AC) and 11% (AT). These symptoms may have influenced the lack of appetite: 25% (AC) and 11% (AT), which resulted in a loss of body mass observed in 6% (AC) and 22% (AT) of the patients. Skin reactions were observed in the form of: dry epidermis exfoliation (II°) in 19% (AC) and 22% (AT), elbow and knee skin itching in 12% (AC) and onycholysis in 11% (AT). Hypersensitivity reactions:

- conjunctival burning sensation - 6% (AC),
- dyspnoea – 12% (AC),
- fever – 31% (AC), 22% (AT) – the highest registered value was 38.5°C (AT),
- urticaria on the face and chest – 6% (AC) – a patient with an aspirin allergy and Hashimoto's disease;
- facial reddening - 6% (AC) – a patient with an aspirin allergy and Hashimoto's disease.

Reported menstruation disorders occurred in 25% of the patients (aged 30-51 years) treated with the AC scheme and in 33% of the patients (aged 31-46 years) treated with the AT scheme.

The literature data presenting the toxic drug reactions from randomised investigations from large clinical centres show only degrees III/IV of toxicity [15]. They do not concentrate on profile I/II, whose frequency of occurrence was relatively high during the monitoring of the patients with locally advanced breast cancer in the Department of Chemotherapy, Oncological Clinic. The data obtained from the aforementioned Department only contains the reports on observations of alopecia and leucopoenia III/IV°.

When monitoring adverse reactions we take into consideration not only unknown adverse reactions, but also those which have been observed already, because this way we obtain the profile of the frequency of occurrence of a particular adverse reaction. It is impossible to speak of the safety of a therapy without the monitoring and evaluation of the information concerning adverse drug reactions. The lack of ADR observation on animals in preclinical examinations does not guarantee the safety of application of new drugs to people. Clinical examinations are carried out in standardised conditions, which diverge from everyday medical practice. The observation of distant reactions to the influence of a therapeutic substance on the organism

is limited by the time regime of an experiment. In clinical examinations adverse drug reactions are found, which occur frequently and depend on the mechanism of reaction. Unfortunately, the reactions which are an effect of drug interactions or an interaction of a drug with food, rarely occurring ADRs, reactions not related with the mechanism of the effect of a drug can only be observed when the drug is used in medical practice [16]. For example, to find the symptoms occurring once in three thousand cases the drug must be administered to 10,000 patients [17]. The introduction of a pharmaceutical preparation into medical practice involves its application to elderly people, paediatric patients, patients with concomitant diseases, various eating habits and addictions, different physical activity and proneness to specific risk factors [16,17].

In recent years there has been an increase in the number of reports on adverse drug reactions. However, there is still a big gap between Poland and West European countries. The Department for Monitoring Adverse Reactions to Therapeutic Products (WMNDPL) in Warsaw receives several hundred reports every year. In 2000 WMNDPL received about 180 spontaneous reports and data from pharmaceutical companies. In 2003 WMNDPL received fewer than 90 spontaneous reports, but about 600 reports from the companies. Thus the number of reports from pharmaceutical companies increased considerably. According to the pharmaceutical law in force a manufacturer is obliged to monitor and report adverse reactions to its own products. However, in comparison with the number of reports on adverse reactions abroad, which are made by companies (even as many as several thousand reports a year), we can see the differences in reporting drug reactions by Polish and foreign doctors.

The occurrence of an adverse drug reaction very often involves the need to increase the costs of patient treatment. Adverse effects of a drug therapy considerably prolong the hospitalisation time. In Moore's research it was found that the average hospitalisation time of each of the 10 patients in whom adverse reactions to pharmacotherapy were observed was 15.1 days. A patient without ADR symptoms was hospitalised for 10.7 days respectively. Other research findings show that the average hospitalisation time of patients with ADRs is 13-10.6 days in Germany and 10.6 days in the USA [18,19].

In view of the widespread character of adverse reactions it seems important that pharmacists and physicians should cooperate to monitor adverse drug reactions. A direct interview with the patient before chemotherapy also enables the registration of those patients who take other drugs, e.g. plant drugs. Phytotherapy is considered a safe alternative to conventional therapy. Therefore, it is especially in this group of patients that a considerable increase in the consumption of plant drugs can be observed [20]. The interactions of these drugs with chemotherapeutics may contribute to the occurrence of adverse reactions or the inefficaciousness of the therapy [21], but they may also reinforce the effect of basic drugs. An example of this could be the interaction of *Hypericum perforatum* with irinotecan [22], *Silybum marianum* with doxorubicin [23], carboplatin and cisplatin [24].

ADR registration may contribute to increased safety of pharmacotherapy, especially if it is done at the moment of occurrence rather than retrospectively. In the current situation of health service when the doctor has no time to constantly monitor and register adverse drug reactions cooperation with a clinical pharmacist may considerably improve the supervision of pharmacotherapy, especially in the groups of patients who are particularly predisposed to the occurrence of drug-induced complications.

Adres do korespondencji:
Edyta Szałek
Katedra i Zakład Farmacji Klinicznej
i Biofarmacji, Uniwersytet Medyczny w Poznaniu
ul. Św. Marii Magdaleny 14; 61-861 Poznań
Phone: (+48 22) 627 39 86, E-mail: czechow73@wp.pl

Piśmiennictwo

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