Pharmacological Reports
2011, 63, 149–156
ISSN 1734-1140

Influence of anticancer therapy on oxidation phenotype and acetylation phenotype in patients with acute myeloblastic leukemia

Łukasz Łapiński[1], Krystyna Orzechowska-Juzwenko[1], Anna Wiela-Hojeńska[1], Dariusz Wołowiec[2], Grzegorz Ganczarski[2], Krystyna Głowacka[1], Henryk Czarnik-Matusewicz[1], Kazimierz Kuliczkowski[2], Jacek Gąsiorowski[3]

[1]Department of Clinical Pharmacology, Wroclaw Medical University, Bujwida 44, PL 50-345 Wrocław, Poland

[2]Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wybrzeże L. Pasteura 5, PL 50-367 Wrocław, Poland

[3]Department of Infectious Diseases, Hepatology and Acquired Immune Deficiencies, Wroclaw Medical University, Koszarowa 5, PL 51-149 Wrocław, Poland

Correspondence: Łukasz Łapinski, e-mail: llapin@farmklin.am.wroc.pl

Abstract:
The aim of this study was to determine whether antineoplastic cytostatic therapy induces changes in the oxidation or acetylation phenotypes in patients with acute myeloblastic leukemia (AML).
The investigations involved 22 patients with AML undergoing chemotherapy with daunorubicin, cytosine arabinoside, etoposide and mitoxantrone. The oxidation phenotype prior to therapy and after termination of induction was examined in all 22 patients and was examined in 10 patients after termination of the first consolidation cycle. The acetylation phenotype was examined prior to therapy and after termination of induction in 21 patients and after termination of the first remission consolidation cycle in 9 patients. The oxidation phenotype was determined by means of the method by Eichelbaum and Gross. The acetylation phenotype was determined using Varley's modification of the Bratton-Marshall method.
Anticancer therapy affected the oxidation phenotype, causing decreased activity of the cytochrome P450 isoenzyme CYP2D6. This decrease suggests that daunorubicin, cytosine arabinoside, etoposide and mitoxantrone may impair the metabolism of other active substances metabolized by this isoenzyme, which should be taken into consideration in planning the dosage scheme in individual patients and considering interactions between drugs. Evaluation of the effect of administered cytostatic drugs on acetylation phenotype revealed no statistically significant decrease in the rate of sulfadimidine acetylation.

Key words:
acute myeloblastic leukemia, AML, oxidation phenotype, acetylation phenotype, genetic polymorphism, anticancer therapy

Introduction

The number of patients who are permanently cured from cancer increases year by year due to earlier diagnosis of the disease and progress in treatments. In 2001, in the USA alone, 3.5% of the whole population, i.e., almost 10 million people, were cured from cancer. Thirty years ago, the number amounted to merely 3 million. The increasing number of people cured from cancer is possible due to contemporary medicine including new and more selective drugs and also old treatment schemes that have been perfected

to take into account physiological specificity of individual patients, diurnal rhythm, associated diseases and genetic factors. Unfortunately, contemporary therapy for acute myeloblastic leukemia (AML) based on the use of cytosine arabinoside and anthracycline antibiotics provides complete remission in 60–80% of patients aged 55–60 years. A five-year survival rate is achieved in 30–40% of patients, despite post-remission therapy. In patients more than 55–60 years of age, complete remission is achieved in 44–55%, and long-term survival is achieved in only 10–15%. In both groups, the majority of patients die due to resistance of AML to the cytostatic drugs used in therapy or due to recurrence of the disease [9, 10, 15]. Failure to treat and death of the patients are significant adverse effects following administration of a standard dose of anticancer drugs. The incidence of these adverse effects may be associated with individual, genetically conditioned reactions to drugs. Knowledge of drugs, especially of cytostatics, which are characterized by a low therapeutic index and insufficient selectiveness in their action on cancer cells, will enable optimization of the therapy for AML [13, 17].

Biotransformation is the stage of drug action in the organism that is most commonly modified genetically. Among numerous enzymes participating in the metabolism of xenobiotics, the cytochrome P450 CYP2D6 gene polymorphism, responsible for the process of oxidation, is the one that has been studied most extensively. Although it constitutes about 2% of the total number of all hepatic isoenzymes, it takes part in the metabolism of as many as 30% of all clinical drugs, including those used in supportive treatment of anticancer chemotherapy, such as the antiemetic ondansetron. Patients who are extensive metabolizers more often develop adverse effects such as nausea, vomiting and limitation of life activity, which are more intense than in intermediate or poor metabolizers. On the other hand, the effect of antiemetic therapy is statistically significantly higher in poor metabolizers than in extensive metabolizers. Additionally, the rate of O-demethylation of codeine and tramadol to active metabolites depends on the CYP2D6 genetic polymorphism. The amount of morphine formed from codeine is much lower in poor metabolizers than in intermediate or extensive metabolizers. Poor metabolizers should be administered significantly higher doses of codeine due to the lower effectiveness of the applied analgesic therapy. Additionally, the process of acetylation, which is part of phase II metabolism, should be considered. This process is catalyzed by N-acetyltransferase (NAT) and controlled by NAT2 genes [3, 7, 11, 13].

The aim of the current study was to determine whether anticancer therapy with cytostatics affects oxidation or acetylation phenotypes.

Materials and Methods

The evaluation of the effect of anticancer therapy on oxidation phenotype and acetylation phenotype was performed in a cohort of 22 patients with AML who were hospitalized in the Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation of Wroclaw Medical University in 2002–2006. The examinations were performed prior to therapy and 1–4 days after termination of induction and the first remission consolidation cycle.

Patients with AML who were less than 60 years of age in the remission induction phase were administered daunorubicin intravenously at a dose of 50 mg/m^2 body surface area (BSA) on days 1–3, cytosine arabinoside in a continuous intravenous infusion or subcutaneously at a dose of 100 mg/m^2 BSA/24 h on days 1–6 and etoposide in an intravenous infusion at a dose of 100 mg/m^2 BSA on days 1–3. Patients from 60 to 80 years of age were administered the following intravenously: mitoxantrone at a dosage of 7 mg/m^2 BSA on days 1, 3 and 5, cytosine arabinoside at a dosage of 100 mg/m^2 BSA on days 1–7, and etoposide at a dosage of 100 mg/m^2 BSA on days 1–3; or daunorubicin at a dosage of 30 mg/m^2 BSA on days 1–3 and cytosine arabinoside at a dosage of 200 mg/m^2 BSA on days 1–7.

Patients younger than 30 years of age who had at least a 30% decrease in the level of blasts in the myelogram on the 6th day or a 20% decrease in the bone marrow were administered cytosine arabinoside in an intravenous infusion or subcutaneously at a dose of 100 mg/m^2 BSA on days 7–10. Patients older than 30 years of age were administered cytosine arabinoside by the same route and at the same dose on day 7. If the decrease in the level of blasts was less than 30%, patients below 30 years of age were administered cytosine arabinoside in an intravenous infusion at a dose of 1.5 g/m^2 BSA every 12 h on days 7–10. Patients older than 30 were administered cytosine arabinoside

in an intravenous infusion at a dose of 1.5 g/m^2 BSA every 12 h on days 7 and 8.

Next, after about a month, patients who responded to therapy were administered remission consolidation therapy, which included 4 chemotherapy cycles. In the first cycle, patients younger than 30 were administered daunorubicin in an intravenous infusion at a dose of 50 mg/m^2 BSA on days 1–3 and cytosine arabinoside subcutaneously at a dose of 100 mg/m^2 BSA every 12 h on days 1–7. Patients aged from 30 to 60 were administered daunorubicin intravenously at a dose of 45 mg/m^2 BSA on days 1 and 2 and cytosine arabinoside subcutaneously at a dose of 100 mg/m^2 BSA every 12 h on days 1–5. Patients aged 60 to 80 were administered daunorubicin intravenously at 45 mg/m^2 BSA on days 1 and 2 and cytosine arabinoside subcutaneously at 100 mg/m^2 BSA every 12 h on days 1–5.

Oxidation phenotype was determined prior to therapy and after termination of remission induction in 22 patients suffering from AML, including 10 females and 12 males, aged from 20 to 77 years, mean age 57.3 ± 10.3 years, and after termination of the first remission consolidation cycle in 10 patients with AML, including 4 females and 6 males, aged from 33 to 71 years, mean age 57.4 ± 8.2 years.

Acetylation phenotype was determined prior to therapy and after termination of remission induction in 21 patients suffering from AML, including 10 females and 11 males, aged from 20 to 77 years, mean age 56.5 ± 10.6 years, and after termination of the first remission consolidation cycle in 9 patients with AML, including 4 females and 5 males, aged from 21 to 71 years, mean age 48.4 ± 8.16 years.

Patients with hepatic, kidney or circulatory insufficiency that might have disturbed normal organ function and patients taking drugs that might have affected the course of oxidation or acetylation processes were excluded from the studies.

All of the subjects were informed about the aims and methods of the investigation and gave their informed consent. The study protocol was approved by the Bioethics Committee of Wroclaw Medical University.

Oxidation phenotype was determined in urine according to the method by Eichelbaum and Gross [5]. After morning micturition, the fasting subjects were administered 100 mg of sparteine sulfate manufactured by Polfa Kutno or Giullini Pharma. Urine was collected for the next 6 h after the administration of sparteine sulfate. Urine amount was measured, and 50 ml of urine was collected and stored at –20°C until analysis.

The urine levels of sparteine and its metabolites, 2- and 5-dehydrosparteine, were determined with the use of an ELWRO 504 M gas chromatograph and COMPUTER SYSTEM FOR PROCESSING DATA 7.5 manufactured by Metroster.

Metabolic ratio (MR) was determined on the basis of the amount of sparteine and its main metabolites excreted in the urine:

$$\text{Metabolic ratio} = \frac{\text{Level of sparteine excreted in urine}}{\text{Level of dehydrometabolites excreted in urine}}$$

The subjects were divided by MR level into extensive metabolizers (EM; MR < 2.5), intermediate metabolizers (IM; 2.5 ≤ MR < 20) and poor metabolizers (PM; MR ≥ 20). Additionally, very extensive metabolizers (VEM; 0.5 < MR < 1.0) and extremely extensive metabolizers (EEM; MR ≤ 0.5) were distinguished among the EM subjects. MR values of 2.5 and 20 were assumed as border values according to Eichelbaum, who, like a majority of other investigators, used sparteine as a model drug [2, 4, 5, 8, 12].

All of the results were recorded on the Oxidation Phenotype Examination Card, which included the following data: name and surname of the patient, age, gender, body mass, clinical diagnosis, drugs administered to the patient in the last week and last few days, laboratory findings (alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, blood plasma creatinine and urea level), adverse effects observed after administration of sparteine, sparteine metabolic ratio, oxidation phenotype, the signature of the physician ordering the tests and the signature of the examiner.

The acetylation phenotype was determined in urine by Varley's modification of the Bratton-Marshall method [16]. After morning micturition, the fasting subjects were administered 44 mg/kg body weight sulfadimidine (Sulphamethazinum, Polfa). Urine was collected for the next 6 h after administration of sulfadimidine. Urine amount was measured, and 50 ml of urine was collected and stored at –20°C until analysis.

The percentage of acetylated sulfadimidine was calculated on the basis of the amount of sulfadimidine and its acetylated derivative determined by means of the colorimetric method [14, 16]:

$$\% = \frac{S_{AC}}{S_0} \times 100$$

$$S_{AC} = S_0 - S_W$$

S_0 – level of total sulfadimidine; S_W – level of free sulfadimidine; S_{AC} – level of acetylated sulfadimidine.

The group referred to as rapid acetylators (RA) included subjects with more than 70% acetylated sulfadimidine, while slow acetylators (SA) included subjects in whom the urine level of acetylated sulfadimidine was lower than 70% [14].

All of the results were recorded on the Acetylation Phenotype Examination Card, which included the following data: name and surname of the patient, age, gender, body mass, administered dose of sulfadimidine, clinical diagnosis, drugs administered to the patient in the previous week and in the previous 3 days, laboratory findings (alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, blood plasma creatinine and urea level), adverse effects observed after administration of sulfadimidine, percentage of acetylated sulfadimidine, acetylation phenotype, the signature of the physician ordering the tests and the signature of the examiner.

Oxidation and acetylation phenotype were determined in the same subject group. Sparteine sulfate and sulfadimidine were administered simultaneously. According to other authors and ours previous data, there is no interaction between the two compounds, and they can be given at the same time [1].

The findings were collected using MS EXCEL 2002 and analyzed with MS EXCEL 2002 and STATISTICA 5.1 Software Package, StatSoft, Inc. Because the distributions of the sparteine metabolic ratio, percentage of acetylated sulfadimidine and the differences between these values prior to therapy and after termination of induction and the first remission consolidation cycle were not normal, the statistical analyses were performed with the use of non-parametric tests. Depending on the size of the investigated group, the χ^2 test, χ^2 test with Yates modification or bilateral Fischer's test, Kolmogorov-Smirnov test or Wilcoxon rank-sum test was performed. A multiple regression was used to investigate the correlation between patient age, gender, body mass, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, blood plasma creatinine or urea level and MR, percentage of acetylated sulfadimidine and oxidation and acetylation phenotype. In all of the tests, $p < 0.05$ was considered statistically significant.

Results

The nature of the changes in the group of 10 patients whose oxidation phenotype was determined before chemotherapy, after termination of induction and after termination of the first chemotherapy consolidation cycle is presented in Table 1. The incidences of EEM, VEM, EM and IM, as well as the mean values and range of the metabolic ratio of sparteine prior to therapy, after termination of induction phase and after termination of the first chemotherapy consolidation cycle, are presented in Table 2.

The poor oxidation phenotype was not observed in the AML patients examined; all of the subjects were extensive metabolizers of sparteine. The metabolic ratio prior to therapy (0.20 ± 0.80) was significantly ($p <$

Tab. 1. Changes in the oxidation phenotype after termination of induction and the first consolidation cycle

Oxidation phenotype			Number of patients	%
Prior to therapy	After termination of induction chemotherapy	After termination of first consolidation cycle		
VEM	EM	EM	4	40
VEM	EEM	EM	1	10
VEM	IM	EEM	1	10
VEM	EM	VEM	1	10
EEM	IM	VEM	1	10
EEM	EM	VEM	1	10
IM	IM	IM	1	10

EEM – extremely extensive metabolizers; VEM – very extensive metabolizers; EM – extensive metabolizers; IM – intermediate metabolizers

Tab. 2. The incidence of extremely extensive, very extensive, extensive and intermediate oxidation phenotypes and mean metabolic ratio in individual groups of AML patients prior to therapy, after termination of induction and after termination of the first consolidation cycle

Group		Metabolic ratio			Number of patients	%
		$\bar{x}$	± SD	range		
Prior to therapy	EEM	0.38	0.10	0.20–0.5	11*	50
	VEM	0.73	0.16	0.52–0.97	8	36.4
	EM	1.32	0.00	1.32–1.32	1**	4.5
	IM	5.24	3.44	2.82–7.67	2	9.1
	Total	0.20***	0.80	0.20–7.67	22	100
After induction chemotherapy	EEM	0.39	0.07	0.31–0.46	5	22.7
	VEM	0.68	0.04	0.63–0.73	5	22.7
	EM	1.33	0.26	1.01–1.75	8	36.4
	IM	4.54	2.46	2.56–8.05	4	18.2
	Total	1.55	1.10	0.31–8.05	22	100
After first consolidation cycle	EEM	0.37	0.00	0.37	1	10
	VEM	0.71	0.14	0.62–0.87	3	30
	EM	1.32	0.24	1.12–1.72	5	50
	IM	5.12	0.00	5.12	1	10
	Total	1.42	0.80	0.37–5.12	10	100

EEM – extremely extensive metabolizers; VEM – very extensive metabolizers; EM – extensive metabolizers; IM – intermediate metabolizers. * Difference on the border of statistical significance in the incidence of EEM among AML patients prior to therapy in comparison to the status after termination of induction chemotherapy ($p = 0.06$) and statistically significant difference in the incidence of EEM among AML patients prior to therapy and after termination of first consolidation cycle ($p = 0.03$). ** Statistically significant difference in the incidence of EM among AML patients prior to therapy in comparison to the status after induction chemotherapy ($p = 0.02$) and statistically significant difference in the incidence of EM among AML patients prior to therapy and after termination of first consolidation cycle ($p = 0.006$). *** Statistically significant difference in the metabolic ratio prior to therapy and after termination induction chemotherapy ($p = 0.0045$)

0.01) lower than that after termination of the chemotherapy induction phase (1.55 ± 1.10). The incidence of EM among AML patients was significantly lower ($p = 0.02$) prior to therapy (4.5%, 1 person) than after termination of the induction phase (36.4%, 8 subjects), while the incidence of EEM among AML patients was higher prior to therapy (50.0%, 11 persons) than after termination of the anticancer chemotherapy induction phase (22.7%, 5 subjects), but the difference was on the borderline of statistical significance ($p = 0.06$).

In the study group, the oxidation phenotype of 14 subjects changed after termination of induction chemotherapy in comparison to the status prior to therapy. The phenotype was accelerated (change from VEM to EEM) in only 1 case. In the remaining group, 7 patients with EEM changed to VEM (4 subjects), EM (2 subjects) and IM (1 subject), and 6 subjects with VEM changed to EM (5 subjects) and IM (1 subject). The oxidation phenotype of the remaining patients did not change. In this unchanged group, 4 subjects were classified as EEM, 1 was VEM, 1 was EM and 2 subjects were IM.

The differences in the metabolic ratio after termination of the first chemotherapy consolidation cycle and prior to therapy, as well as after termination of induction treatment, did not differ significantly; however, the incidence of EM was significantly lower ($p = 0.006$) among AML patients prior to therapy (4.5%, 1 person), compared to the incidence after termination of the first chemotherapy consolidation cycle (50.0%, 5 patients). On the other hand, the incidence of EEM was significantly higher ($p = 0.03$) among AML patients prior to therapy (50.0%, 11 subjects), compared to the incidence after termination of the first chemotherapy consolidation cycle (10.0%, 1 person).

The incidences of rapid acetylator (RA) and slow acetylator (SA), as well as the mean percentage and range of acetylated sulfadimidine prior to therapy, after termination of induction and after the first chemo-

Tab. 3. Mean value and percentage of acetylated sulfadimidine prior to and after termination of induction chemotherapy in AML patients

Group		Percentage of acetylated sulfadimidine			Number of patients	%
		$\bar{x}$	± SD	range		
Prior to therapy	RA	79.84	4.85	72.03–90.24	8	38
	SA	47.95	9.67	26.85–68.87	13	62
	Total	60.10	16.30	26.85–90.24	21	100
After induction chemotherapy	RA	80.45	5.19	70.19–94.15	6	28.6
	SA	49.92	11.76	27.27–69.09	15	71.4
	Total	58.64	15.39	27.27–94.15	21	100
After first consolidation cycle	RA	73.27	0	73.27	1	11.1
	SA	47.61	11.27	16.67–67.61	8	88.9
	Total	50.46	11.93	16.67–73.27	9	100

RA – rapid acetylator; SA – slow acetylator. No statistically significant differences in the number of RA and SA and in the percentage of acetylated sulfadimidine prior to therapy, after termination of induction chemotherapy and after termination of first consolidation cycle

therapy consolidation cycle, in patients with AML are presented in Table 3. There were no statistically significant differences in the number of RA and SA and in the percentage of acetylated sulfadimidine prior to therapy, after termination of induction chemotherapy and after termination of the first consolidation cycle.

After termination of induction chemotherapy, the acetylation phenotype of 5 patients from the investigated group changed from RA to SA and 3 changed from SA to RA in relation to the status prior to therapy. After termination of the first consolidation cycle in comparison to the status prior to therapy, the acetylation phenotype of 2 patients changed from RA to SA and 1 from SA to RA, whereas in comparison to the status after termination of induction chemotherapy, the acetylation phenotype of 1 patient changed from RA to SA and that of another patient changed from SA to RA.

The number of patients under observation after termination of the first chemotherapy consolidation cycle was low due to high mortality during therapy and an increased incidence of severe adverse effects of the administered cytostatic drugs, such as vomiting, which made determination of the oxidation phenotype impossible.

There were no statistically significant correlations between the patient's age, gender, body mass, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, blood plasma creatinine or urea level and metabolic ratio, percentage of acetylated sulfadimidine, oxidation phenotype and acetylation phenotype prior to therapy, after termination of induction chemotherapy and after termination of the first consolidation cycle.

Discussion

The present study evaluated the effect of administered AML chemotherapy on the oxidation or acetylation phenotype in a group of AML patients. The study was inspired by opinions published in the literature, which have confirmed a toxic effect of currently administered cytostatic drugs on the functioning of both the liver and the kidneys, which are the main organs participating in the elimination of drugs from the organism [17, 18].

Neoplastic disease and therapy with cytostatic drugs may cause both local and general dysfunctions of the whole organism. Currently used anticancer drugs are characterized by low selectivity of action and high, differentiated toxicity. Of special interest from the clinical point of view are the adverse effects associated with impaired functioning of the liver and the kidneys, which are the organs that are responsible for detoxification of the organism. A detailed mechanism of the hepatotoxic effect of cytostatic drugs is not clear in a majority of cases, and the same drug may provoke impairment of hepatocytes in various ways. There are two mechanisms of drug hepatotoxicity: biochemical and immunoallergic, which are not mutually exclusive. A majority of therapeutic agents evoke biochemical reactions. Anticancer drugs impair the synthesis of nucleic acids or proteins. This effect is especially evident in the case of antimetabolites and alkylating agents. Moreover, antimetabolites and alkylating drugs may increase the level of free oxygen

radicals, which damage hepatocyte walls, and, in the case of cytosine arabinoside, impair the endothelium of small hepatic veins, inducing occlusion of the hepatic veins. The area that is significantly affected by pathological lesions after administration of hepatotoxic drugs is situated in the central zone of the hepatic lobules and has the highest concentration of cytochrome P450 s. Damage to the hepatocytes may result in depletion of the total amount of individual cytochrome P450 isoenzymes and deterioration of the metabolic capacity of the liver [17].

Significant damage to the liver results in impaired detoxification of the organism and accumulation of administered active substances, which leads to an increase in the pharmacological activity and at the same time, increases the toxicity of the applied therapy. As a result, the hepatotoxic activity negatively affects the final outcome of treatment; the dose of anticancer drugs has to be decreased or the chemotherapy has to be interrupted temporarily [17, 18].

The usefulness of the present study is substantiated by scarce data in the literature on the functional condition of the liver in patients with AML, who are administered numerous drugs. Determination of the detoxification capacity of the liver in patients with AML is extremely important from the clinical point of view, because it significantly increases the safety of anticancer pharmacotherapy.

Our studies have demonstrated a decrease of sparteine metabolism after termination of the first induction chemotherapy cycle in comparison to the metabolism prior to therapy. However, no statistically significant differences in the metabolic ratio were found after termination of induction chemotherapy, compared with after the termination of the first chemotherapy consolidation cycle. Although none of the oxidation phenotypes of the patients changed from EM to PM, the oxidation status of over 60% of patients changed within the subgroups of EM. The reason for the decreased metabolism of sparteine (increased MR value) may be attributed to the hepatotoxic effect of the administered drugs. However, due to a large number of cytostatics administered in a short period, explicit determination of which substances were responsible for the condition was not possible. The antimetabolite drug cytosine arabinoside was most probably the greatest contributor to the elevated the metabolic ratio. However, the inhibitory or toxic effect of several simultaneously administered drugs cannot be excluded.

Wiela-Hojeńska et al. [18] demonstrated the inhibitory effect of epirubicin and cytarabine or mitoxantrone and cytarabine on phenazone metabolism rate in patients with AML during anticancer chemotherapy. Phenazone is generally recognized as an indicator of the metabolic activity of microsomal enzymes of the liver; it is metabolized by several cytochrome P450 isoenzymes, such as CYP1A2, CYP2C9 and CYP3A4. Investigation of phenazone pharmacokinetics provides information on changes in drug metabolism, but it should be noted that the effect of hepatic diseases on the activity of individual cytochrome P450 isoenzymes varies. CYP3A isoenzymes are most sensitive to pathological changes within the hepatic tissue, while CYP2D6 is the least sensitive [18].

Our studies, together with the findings obtained by Wiela-Hojeńska et al., suggest a damaging effect of the administered anticancer therapy on the whole cytochrome P450 system.

The demonstration of intensive sparteine metabolism in AML patients as well as the decreased activity of cytochrome P450 isoenzyme CYP2D6 during therapy should be taken into consideration in determining new dosage schemes for drugs metabolized by the monooxygenase system. Cytochrome P450 isoenzyme CYP2D6 is particularly important, because it plays an important role in the metabolism of more than 30% of commonly used drugs. The most commonly used cytochrome P450 isoenzyme CYP2D6 substrates are presented in Table 4 [13].

The current study failed to reveal any effect of the applied therapy on the acetylation phenotype. No reports confirming or questioning the findings were found in the available literature. Only Elkira et al. [6] evaluated the acetylation rate during doxorubicin and cyclophosphamide therapy, but their experimental group was composed of patients with breast cancer. Their studies did not demonstrate any effect of the therapy on NAT2 activity.

Conclusions

1. Anticancer chemotherapy with daunorubicin, cytosine arabinoside, etoposide and mitoxantrone caused a decrease in the activity of the cytochrome P450 isoenzyme CYP2D6 suggesting that these cytostatics may also impair the metabolism of many other drugs metabolized by this enzyme. This finding should be

Tab. 4. The most commonly used cytochrome P450 isoenzyme CYP2D6 substrates [13]

Substrates	
Opioids	Codeine, dextrometorphan, tramadol
β-Blockers	Carvedilol, metoprolol, timolol
Tricyclics	Amitriptyline, clomipramine, desimipramine, imipramine, nortriptyline
Selective serotonin reuptake inhibitor	Citalopram, fluvoxamine, fluoxetine, paroxetine
Antipsychotics	Droperidol, haloperidol, risperidone, thioridazine
5-HT_3 receptor antagonists	Ondansetron, tropisetron

considered in planning the dosage schemes in individual patients in the future and predicting interactions between cytostatics and simultaneously administered drugs metabolized by isoenzyme CYP2D6.

2. There was a damaging effect of the administered cytostatics on sparteine metabolic ratio and no change in sulfadimidine metabolism rate, which may indicate different susceptibilities of individual metabolic pathways to the toxic effects of anticancer drugs.

Acknowledgment:
The study was performed as part of Grant No. 1664 from Wroclaw Medical University.

References:

1. Baxter K: Stockley's drug interactions: a source of interactions, their mechanisms, clinical importance and management. Pharmaceutical Press, 8th edn., London, Chicago, 2008.
2. Brosen K, Otton V, Gram LF: Sparteine oxidation polymorphism in Danmark. Acta Pharmacol Toxicol, 1985, 51, 357–360.
3. Donnelly JG: Pharmacogenetics in cancer chemotherapy. Ther Drug Monit, 2004, 26, 231–235.
4. Eichelbaum M: Defective oxidation of drugs. Pharmacokinetics and therapeutic implication. Clin Pharmacokinet, 1982, 7, 1–22.
5. Eichelbaum M, Spannbrucher N, Steincke B, Dengler HJ: Defective N-oxidation of sparteine in a man: a new pharmacogenetic defect. Eur J Clin Pharmacol, 1979, 16, 183–187.
6. Elkiran T, Harputluoglu H, Yasar U, Babaoglu MO, Dincel AK, Altundag K, Ozisik Y et al.: Differential alteration of drug-metabolizing enzyme activities after cyclophosphamide/adriamycin administration in breast cancer patients. Methods Find Exp Clin Pharmacol, 2007, 29, 27–32.
7. Emilien G, Poncho M, Caldas C, Isacson O, Malotreaux JM: Impact of genomics on drug discovery and clinical medicine. QJM, 2000, 93, 391–423.
8. Gonzales PJ, Meyer UA: Molecular genetics of the debrisoquine-sparteine polymorphism. Clin Pharmacol Ther, 1991, 50, 233–238.
9. Hoelzer D, Gokbuget N, Ottmann O, Pui CH, Relling MV, Appelbaum FR, van Dongen JJM, Szczepański T: Acute lymphoblastic leukemia. Hematology, 2002, 32, 162–192.
10. Licht JD, Tallman MS, Cornelissen JJ: Acute myeloid leukemia. Hematology, 2005, 65, 137–142.
11. Lötsch J, Skarke C, Liefhold J, Geisslinger G: Genetic predictors of the clinical response to opioid analgesics. Clin Pharmacokinet, 2004, 43, 983–1013.
12. Niewiński P, Orzechowska-Juzwenko K, Hurkacz M, Rzemisławska Z, Jaźwińska-Tarnawska E, Milejski P, Forkasiewicz Z: CYP2D6 extensive, intermediate and poor phenotypes and genotypes in a Polish population. Eur J Clin Pharmacol, 2002, 58, 533–535.
13. Niewiński P, Orzechowska-Juzwenko K, Milejski P: Pharmacogenetics (Polish). In: Clinical Pharmacology. Significance in Clinical Practice. Ed. Orzechowska-Juzwenko K, Górnicki, Wydawnictwo Medyczne, Wrocław, 2006, 145–161.
14. Rao KVN, Mitchison DA, Nair NGK, Prema K, Tripathy SP: Sulphadimidine acetylation test for classification of patients as slow or rapid inactivators. Br Med J, 1970, 3, 495–497.
15. Travis LB: Cancer survivorship: understanding risk. 42nd Annual Meeting American Society of Clinical Oncology, June 2–6 2006. Education Book, 520–522.
16. Varley H: Drugs and poisons. Sulphonamides. In: Practical clinical biochemistry. Ed. Varley H, Heinemann, London, 1962.
17. Wiela-Hojeńska A, Orzechowska-Juzwenko K: Adverse drugs reaction (Polish). In: Clinical Pharmacology. Significance in Clinical Practice. Ed. Orzechowska-Juzwenko K, Górnicki, Wydawnictwo Medyczne, Wrocław, 2006, 209–246.
18. Wiela-Hojeńska A, Orzechowska-Juzwenko K, Usnarska-Zubkiewicz L, Kotlarek-Haus S, Hurkacz M: Phenazone as a marker of liver-metabolic function in patients with acute leukemia. Int J Clin Pharmacol Ther, 1999, 37, 234–237.

Received: August 26, 2009; **in the revised form:** August 4, 2010; **accepted:** September 21, 2010.