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ORIGINAL ARTICLE

Significance of OCT1 Expression in Acute Myeloid Leukemia

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Abstract Organic cation transporter 1 (OCT1) is one of the membrane proteins in the large solute carrier (SLC) family. It participates in the transport of organic cations, i.e. nutrients, neurotransmitters, metabolites or drugs in an electrogenic manner and translocate various cationic cytostatics. Knowledge concerning the expression of drug transporters in tumor cells may help to develop cytotoxic agents that are targeted to specific tumors. OCT1 expression and its relationship to the proliferation of cancer cells, development of metastases and resistance to chemotherapy has been observed in solid tumors. There is no data concerning the significance of OCT1 expression in the clinical course and treatment results in acute myeloid leukemia (AML). The objective of the study was firstly to evaluate *OCT1 mRNA* expression in patients with newly diagnosed de novo AML, and secondly to compare the obtained results to the healthy control group as well as analyze them according to leukemia subtypes, CD34 expression, cytogenetic and molecular factors and treatment results. 101 patients with AML, excluding the subtype classified as M3 by French-American-British (FAB) criteria, were analyzed. The control group consisted of 26 healthy individuals. The evaluated material was bone marrow (BM). Real-time quantitative polymerase chain reaction (RQ-PCR) was used in the study as a method of evaluating *OCT1 mRNA* expression. The study showed a statistically significant lower expression of *OCT1 mRNA* in patients with AML in comparison to the control group. The level of *OCT1 mRNA* expression was lowest for CD34+ leukemia. No significant correlation between *OCT1 mRNA* expression and cytogenetic and molecular factors was observed. A significant influence of *OCT1 mRNA* expression on the clinical outcome of the disease was observed: patients with lower expression had higher chances of achieving complete remission (CR) and longer overall survival (OS).

Keywords Acute myeloid leukemia · OCT1 · Resistance to chemotherapy

Introduction

Acute myeloid leukemia (AML) is a hematological malignancy that begins during the early development stages of myeloid cells [1]. Despite intensive chemotherapy the results of AML treatment are still unsatisfactory. Standard induction protocols make it possible to achieve complete remission only in a fraction of patients, and in only a very small percentage of patients is long relapse-free survival observed. One of the major reasons for the failure of chemotherapy is drug resistance. This is a multifactor phenomenon and includes various mechanisms such as increased drug inactivation, enhanced repair of chemotherapy-induced damage, activation of pro-survival pathways and disturbance in the transmembrane transport involving ATP-dependent polyspecific transporters of the ATP binding cassette (ABC) family or solute carrier family 22 (SLC22) [2, 3]. The SLC22 family comprises organic cation transporters (OCTs), zwitterion/cation transporters (OCTNs), and organic anion transporters (OATs). OCT1 is coded by the *SLC22A1* gene located on the long arm of chromosome 6 (6q26) [4]. Under physiological conditions, the transporter shows overlapping sites of expression in many tissues such

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as the intestine, liver, kidney, heart, skeletal muscle, placenta, lung, brain and immune system cells. OCT1 has also been found on the surface of solid tumor cells [5]. This membrane protein is not specific to one substrate. It participates in the transport of organic cations, i.e. drugs, toxins or endogenous compounds in an electrogenic manner, and mediates the absorption of cationic cytotoxic agents into cancer cells. Many compounds inhibit or modulate the transport activity of OCT1 and not all of them are transported substrates [3, 6]. The expression of this transporter could be disturbed in various disease states. Reduced activity of OCT1 has been reported in chronic renal failure and cholestasis [7, 8]. Knowledge concerning the expression of drug transporters in tumor cells may help to develop cytostatic drugs that are targeted to specific tumors. Resistance to chemotherapy may result from the decreased activity of these proteins or intermediary mechanisms that determine sensitivity to chemotherapy such as delivering nutrients to cancer cells or modulating a transmembrane electrochemical gradient, which may distort the response to chemotherapy. This leads to changes in the process of apoptosis and ineffective diffusion of cytotoxic agents into the cell along the electrochemical gradient [5, 9, 10]. OCT1 expression and its relation to resistance to chemotherapy has been observed in solid tumors as well as in the some hematological malignancies. OCT1 plays a key role in the uptake and cytotoxicity of platinum derivatives in colorectal tumors or bendamustine in chronic lymphocytic leukemia (CLL) [10, 11]. Moreover, the expression and activity of *OCT1 mRNA* are important determinants of cytogenetic and molecular response to imatinib in chronic myeloid leukemia (CML) [12–15]. Correlation between the expression of *OCT1 mRNA* and response to chemotherapy in acute leukemias has not been evaluated. It is known that OCT1 participates in mediation absorption of mitoxantrone [16], however there is no data defining the role of this protein in the transport of other anthracyclines or cytosine arabinoside, which are used in the induction therapy for AML. This study evaluated *OCT1 mRNA* expression in patients with newly diagnosed AML. The results were compared to the healthy control group and analyzed according to leukemia subtypes, CD34 expression, cytogenetic and molecular factors, and treatment results such as achieving complete remission (CR), relapse-free survival (RFS) and overall survival (OS).

Materials and Methods

Patients

101 non-M3 AML patients were included in this study: 58 men and 43 women with the median age at diagnosis of 49 years (range 19–84 years). All patients had newly diagnosed de novo AML and were diagnosed between 2000 and 2010 at the

Table 1 Clinical characteristic of AML patients

Number of patients	101
Age	49 (19–84)
Sex	F- 43; M -58
FAB, *n*	
M0	8
M1	20
M2	23
M4	31
M5	16
M6	3
WHO 2008, *n*	
Acute myeloid leukemia with recurrent genetic abnormalities	18
Acute myeloid leukemia with multilineage dysplasia	5
Acute myeloid leukemia not otherwise categorized	78
Cytogenetic group, *n*	
Favorable	21
Intermediate	48
Adverse	32
Molecular changes, *n*	
FLT3-ITD	22
NPM1-mut	31
Median white blood cells count (10^9/L)	30 (0.52–509)
Median platelet count (10^9/L)	52 (5–433)
Median hemoglobin level (g/dL)	9 (5.5–15.1)
LDH (U/l)	709 (180–13,53-4)
Blast cells in bone marrow (%)	75 (20.5–97)
CD 34^+ , *n*	61
Treatment, *n*	
a) ≤ 60 yrs. (*n* = 76)	
DA	35
DAC	25
DAF	9
Palliative treatment	7
b) > 60 yrs. (*n* = 25)	
DA	15
Ara-C + mitoxantron	2
Low dose of Ara-C	3
Low dose of decitabine	2
Palliative treatment	3
Response to treatment, *n*	
CR	57
NR	44

F-female, *M*-male, *LDH* lactic acid dehydrogenase, *MDS* myelodysplastic syndrome, *FAB* French, American, British Co-operative group, *CR* complete remission, *NR* non response, *Ara-C* cytarabine arabinoside, *DA* daunorubicin + cytarabine arabinoside, *DAF* daunorubicin + cytarabine arabinoside + fludarabine, *DAC* daunorubicin + cytarabine arabinoside + cladribine, *WHO* World Health Organisation

Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation at the Medical University in Wrocław, Poland. Bone marrow (BM) samples were evaluated prior to the initiation of induction therapy. Informed consent from all patients and healthy individuals was obtained according to the Declaration of Helsinki and approved by decisions of the local ethics committee at Wrocław Medical University. The subtypes of AML were classified based on French-American-British (FAB) classification criteria [17]. World Health Organization (WHO) classification was also used [18], however, due to the number of patients in the particular subtypes, FAB criteria were applied for statistical purposes. Using European Leukemia Net (ELN) recommendations, patients were categorized into three cytogenetic groups: favorable, intermediate and adverse risk [19]. Cytogenetic tests were performed in the Hematology Cytogenetics Lab at the Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation at Wrocław Medical University. The clinical characteristics of all AML patients are summarized in Table 1.

Patients ≤60 yrs. (n = 76) were treated according to the Polish Adult Leukemia Group (PALG) induction protocols which consist of administering daunorubicin and the conventional dose of cytarabine arabinoside (Ara-C) [20, 21]: Patients >60 yrs. (n = 25) were treated according to the PALG or Cancer and Leukemia Group B (CALGB) protocols [22, 23]. In three patients older than 60 years, we administered a low dose of Ara-C and in two patients, decitabine. Seven of 76 patients ≤60 yrs. and three of 25 patients >60 yrs. received only palliative therapy due to poor performance status and comorbidities. Response criteria were assessed based on ELN recommendations [19]. The control group consisted of 26 healthy individuals: 17 men and 9 women with the median age of 46 years (range: 22–74 years).

Methods

BM samples from 101 patients and 26 healthy individuals were obtained. Mononuclear cells from the BM samples were isolated by gradient separation using Gradisol L (Aqua Medica, Łódź). RNA was extracted using a TriReagent® kit (Ambion/Applied Biosystems, Warszawa). In a 20 μl reaction, 2 μl of total RNA was reverse transcribed using a High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Warszawa). The mRNA levels of OCT1 and beta-glucuronidase-GUS (control gene) were measured by real-time quantitative polymerase chain reaction (RQ-PCR) based on TaqMan Gen Expression Assays (Applied Biosystems): Hs00427550_m1 for OCT1 and Hs99999908_m1 for GUS. RQ-PCR was performed in duplicate and carried out on the 7500 Real Time PCR System (Applied Biosystems) using the TaqMan Gene Expression Master Mix (Applied Biosystems). The amount of complementary DNA (cDNA) used in the reaction corresponded to 50 ng of isolated RNA. The relative quantitation was indicated by threshold cycle (CT) values and determined based on the reaction for the target and control gene. The measure of mRNA expression was the difference (ΔCT) between the CT for the OCT1 gene and the CT for the GUS control gene (ΔCT = CT OCT1 - CT GUS). The relative expression level was determined as $2^{-\Delta CT}$ according to Applied Biosystems.

Statistical Analysis

Statistical analysis was performed using STATISTICA software, version 9.0. The chi-square test of independence was used to determine the relationship between two categorical variables. For a small number of groups, Fisher's exact test and Yates's correction test were used. Pearson's correlation was used to evaluate the correlation between paired values. Due to the presence of outliers, in some cases the Spearman's rank correlation coefficient was used. Statistical comparisons

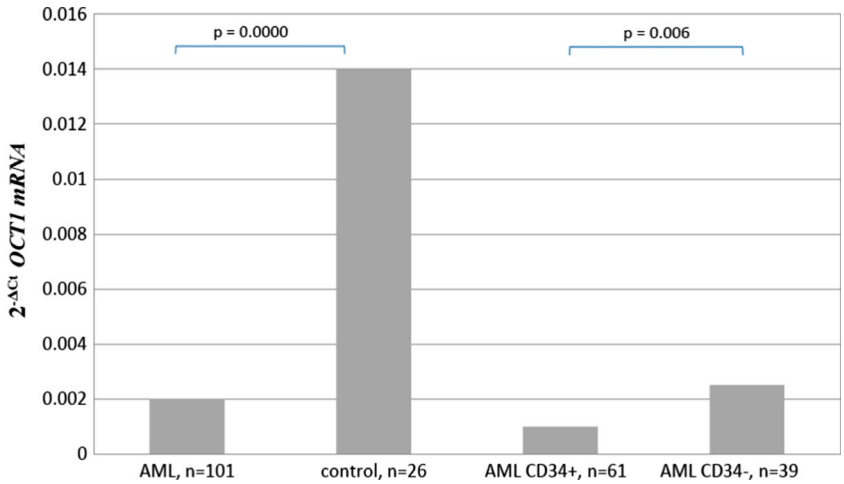

Fig. 1 Expression of *OCT1 mRNA* in AML, AML CD34+, AML CD34- and in control group

between groups were performed by means of the Mann-Whitney U-test (non-parametric analysis) and ANOVA rang Kruskal-Wallis test. A p-value <0.05 indicated a statistically significant difference.

Results

Expression of *OCT1 mRNA* in All AML Patients, in AML CD34+ Patients, in AML CD34- Patients and in Control Group

The level of *OCT1 mRNA* expression was measured in all 101 patients with AML and 26 individuals in the control group. In patients with AML a statistically significantly lower *OCT1 mRNA* expression compared to the control group (0.002 ± 0.004 vs 0.014 ± 0.0129; $p = 0.000$) was observed. Moreover, patients with CD34+ leukemia showed a visibly lower *OCT1 mRNA* level compared to $CD34^{-}$ patients (0.0010 ± 0.0013 vs 0.0025 ± 0.0030; $p = 0.006$). The results are shown in Fig. 1.

OCT1 mRNA Expression and Clinical Characteristics of AML Patients

The analysis included the following parameters: leukocyte count, lactate dehydrogenase (LDH), percentage of BM blast cells and patients' age (Table 2). It was observed that the average value of *OCT1 mRNA* increases with age, but no significant correlation between *OCT1 mRNA* expression and the remaining factors was observed. Additionally, the patients were divided into four groups, based on FAB morphological criteria: Group 1 - AMLs M0 and M1; Group 2 - AML M2; Group 3 - AMLs M4 and M5; Group 4 - AML M6. The statistical analysis did not include patients with the M6 subtype (group 4), due to the small number of patients in the group ($n = 3$). The analysis did not show any statistically significant differences in *OCT1 mRNA* expression in the different groups of patients with AML.

Table 2 Relationship between *OCT1 mRNA* expression and clinical characteristic of AML patients

	OCT1 mRNA	
	r	*p*-value
leukocyte	- 0.089	NS
LDH	- 0.116	NS
Bone marrow blast (%)	- 0.177	NS
Age	0.206	**$p \leq 0.05$**

LDH lactate dehydrogenase, *r*- Spearman's rank correlation, *NS* no significant

Table 3 Correlation between *OCT1 mRNA* expression and cytogenetic risk groups

Cytogenetic group	$n = 101$	*OCT1 mRNA*	
		H-statistic	*p*-value
AR	32	2.99657	$p = 0.2235$
IR	48		
FR	21		

AR adverse risk, *IR* intermediate risk, *FR* favourable risk

Correlation between *OCT1 mRNA* Expression and Cytogenetic and Molecular Factors

OCT1 mRNA expression in patients with AML is also related to cytogenetic risk according to the ELN [17]. Out of the 101 patients participating in the study, 32 patients were at adverse risk (AR), 21 at favorable risk (FR) and 48 at intermediate risk (IR). There was no statistically significant difference in *OCT1 mRNA* expression between all cytogenetic risk groups (Table 3). Mutations in the nucleophosmin 1 (NPM1) gene and internal tandem duplications of the fms-like tyrosine kinase 3 (FLT3) gene were analyzed. No statistically significant differences in *OCT1 mRNA* expression with respect to the mutant (mut) and wild type (wt) forms of the FLT3 gene or the NPM1 gene were found (Table 4).

Correlation between *OCT1 mRNA* Expression and Clinical Outcome

OCT1 mRNA expression was compared to clinical outcomes such as response to induction chemotherapy, RFS, CR and OS. It was observed that patients who achieved CR_I after the induction treatment showed a significantly lower *OCT1 mRNA* expression compared to non-response (NR) patients ($p = 0.030$). This analysis did not include 15 patients who received palliative treatment and a low-dose of Ara-C or decytabine (Table 5). There was no statistically significant difference in the level of *OCT1 mRNA* expression in patients remaining in CR ($n = 24$) compared to patients who had a relapse ($n = 26$) (0.0014 ± 0.0010 vs 0.0038 ± 0.0069; $p = 0.466$). Finally, *OCT1 mRNA* expression correlated negatively with OS and this correlation was statistically significant ($r = -0.2066$; $p \leq 0.05$) (Fig. 2).

Table 4 Correlation between *OCT1 mRNA* expression and molecular factors

	FLT3-ITD			NPM 1		
	$n = 101$	Z-statistic	*p*-value	$n = 101$	Z-statistic	*p*-value
wt	79	-0.0123	$p = 0.9901$	70	1.1449	$p = 0.2522$
mut	22			31		

Table 5 *OCT1 mRNA* expression according to induction response

Response to induction therapy	*n* = 86	*OCT1 mRNA* (x ± SD)	*p*-value
CR	57	0.0014 ± 0.0020	***p* = 0.030**
NR	29	0.0038 ± 0.0069	

CR complete remission, *NR* non response, x-mean, *SD* standard deviation

Discussion

OCT1 is one of the carrier proteins in the SLC family and is subject to expression both in healthy tissues and on the surface of many solid cancers. Currently, there is not much data available concerning the evaluation of SLC proteins in healthy hematopoietic cells and hematological malignancies. However, OCT1 expression has been confirmed in neutrophils, basophils, lymphocytes and monocytes. In one study, it was shown that the highest expression and activity of *OCT1 mRNA* is present in neutrophils, while the lowest is characteristic of lymphocytes [6]. These findings referred to both normal peripheral blood as well as the blood of patients with CML. Kobayashi et al. analyzed BM and proved that *OCTN1 mRNA* expression is present in the myeloid, and not in the lymphoid cell line [24]. In our study, we observed *OCT1 mRNA* expression both in healthy BM and in the BM of patients with AML. This suggests that *mRNA* expression for SLC proteins, including OCT1, is manifested in normal hematopoietic cells and in myeloid growths. The patients with acute leukemia that we examined showed a significantly lower level of *OCT1 mRNA* expression compared to the control group. Similar results have been found in patients with myelodysplastic syndrome, where a significantly lower level of *OCTN2 mRNA* from the SLC family was observed compared to healthy controls [25]. Bazeos et al. found lower *OCT1 mRNA* expression in the peripheral blood of patients with CML compared to the healthy population [26, 27]. This data may point to the fact that *OCT1 mRNA* expression is impaired in cancers of the myeloid lineage, including AML. The presence of leukemic stem cells (LSC) in the BM after induction treatment suggests resistance to cytotoxic drugs and the possibility of a relapse. Considering the fact that SLC proteins, including OCT1, mediate the transport of cytotoxic agents into cells, it would be useful to examine their expression in leukemic stem cells. Engler et al. found *OCT1 mRNA* expression in primitive CD34+ cells in CML. The expression was significantly lower compared to CD34- cells [28]. By analogy, in our analysis *OCT1 mRNA* expression was demonstrated both in patients with CD34+ and CD34- AML, and it was significantly lower in the CD34+ population. When looking at the data in which the presence of CD34+ cells is related to lower *OCT1 mRNA* expression, it would be reasonable to expect lower *OCT1 mRNA* expression in patients with AML M0 and M1. Indeed, the lowest *OCT1 mRNA* expression was observed in patients whose cancer clone consisted of cells classified as M0 and M1 according to FAB criteria. We can therefore conclude that *OCT1 mRNA* expression may be related to the maturation of the myeloid line cells. A previous study confirmed that along with the differentiation of cells from blast forms to mature granulocytes, there is an increase of OCT1 expression [6]. We observed a correlation between *OCT1 mRNA* expression in BM and response to induction treatment. Patients with acute leukemia who achieved CR had a significantly lower level of *OCT1 mRNA*. Additionally, *OCT1 mRNA* expression was higher in patients who relapsed compared to patients who remained in CR after the induction treatment. However, the difference was not statistically significant. We also found a correlation between *OCT1 mRNA* and the OS of patients with AML. Patients with a lower level of *OCT1 mRNA* had a markedly longer survival compared to patients with higher *OCT1 mRNA* expression and the correlation was statistically significant. These results differ from some data found in literature, where lower *OCT1 mRNA* expression correlated with worse response to treatment, e.g. in the case of colorectal cancer or CML [10, 15]. Some

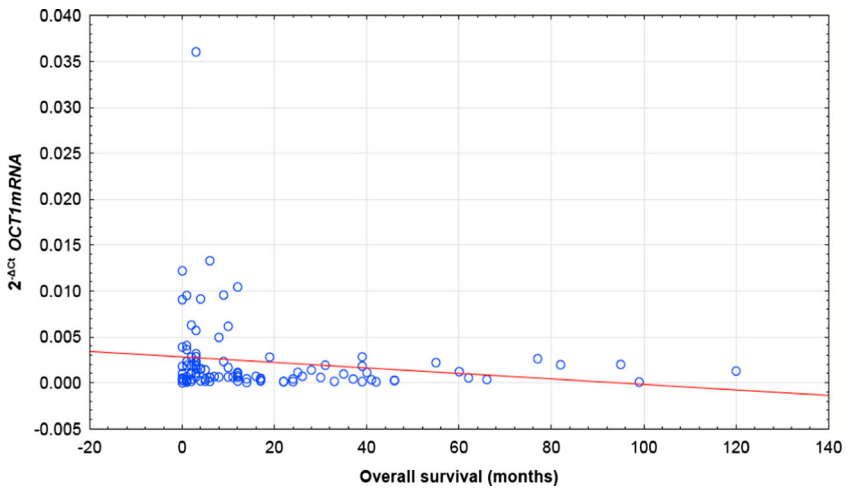

Fig. 2 *OCT1 mRNA* and overall survival

publications found no correlation between *OCT1 mRNA* expression and treatment response. Razga et al. evaluated the BM and peripheral blood of patients with CML treated with imatinib and did not observe any significant connection between *OCT1 mRNA* level before therapy and response to treatment after 6 and 12 months. What is more, in both of these time frames, considerably large groups of patients had an optimal response to treatment, regardless of the low initial *OCT1 mRNA* expression [29]. Similar results were obtained by White et al. in a larger study, where the frequency of optimal responses to imatinib treatment was related to low *OCT1 mRNA* expression before treatment [30]. The above data suggests that it is possible to achieve remission in some patients irrespective of the initial *OCT1 mRNA* expression. What has to be emphasized is that both the expression and the activity of OCT1 may be modulated by a number of factors, which include polymorphism in the SLC22A1 gene that codes OCT1. Additionally, the impact of molecular disorders on OCT1 activity has been studied. It was found that in patients with CML, the presence of the *bcr-abl* fusion gene does not directly affect the level of *OCT1 mRNA* expression and the activity of this protein [6]. Our study did not show any significant differences in the level of *OCT1 mRNA* in groups with different cytogenetic risks, as well as with respect to mutations of the FLT3 and NPM1 genes. We also observed that the level of SLC protein expression may differ with respect to age, which is one of the prognostic factors in AML [24]. Our study showed a positive correlation between the age of the patient and *OCT1 mRNA* level. Considering the fact that young age is a positive prognostic factor in AML, this correlation may indirectly explain the connection between low *OCT1 mRNA* expression and better response to treatment combined with better clinical outcome.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interest regarding the publication of this article.

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