Original Paper

Assessment of Oxidative Stress in Patients with Chronic Myeloid Leukemia Depending on Associated Comorbidities

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ABSTRACT: Oxidative stress (OS) implies an imbalance between the amount of tissue level of prooxidant and antioxidant compounds. It is involved in the pathophysiology of multiple pathological entities (neoplasms, disorders of carbohydrate and lipid metabolism, cardiovascular and renal pathology etc.), as well as in the pharmacokinetics of specific treatments for these pathologies. Chronic myeloid leukemia (CML) is a chronic myeloproliferative disease for which current standard treatment is BCR-ABL tyrosine kinase inhibitors (TKIs). It is known that OS is involved in CML pathogenesis and response to TKIs therapy, but in reality, there are a number of additional factors (associated comorbidities, specific therapies) that modulate oxidative status, possibly affecting the evolution and prognosis of CML. In the present paper we proposed the evaluation of OS in a group of patients with CML following treatment with TKIs, depending on the presence of comorbidities and associated treatments. There were considered associated comorbidities: diabetes mellitus, dyslipidemia, arterial hypertension, heart failure, chronic kidney disease. The variability of the oxidative status was found depending on the type of associated comorbidity, but also according to the associated treatment, with the possibility of producing drug interactions between the standard treatment of CML and the associated specific therapies. Their impact on the prognosis of CML patients in treatment with TKIs is not negligible and may represent a future research topic.

KEYWORDS: *Reactive oxygen species, antioxidant capacity, chronic myeloid leukemia, comorbidity.*

Introduction

Reactive oxygen species (ROS) (superoxide, hydroxyl, hydrogen peroxide) are generated during normal aerobic metabolism, mostly at the mitochondrial level, being produced by cells such as: macrophages, neutrophils, endothelial cells, epithelial cells [1].

Reduced levels of ROS are useful in normal cellular activity, but an excessive amount of free radicals becomes harmful to nucleic acids, lipids and cellular proteins [2].

OS (oxidative stress) results from the imbalance between prooxidants and antioxidants in favour of prooxidants [3].

ROS have a dual role in the pathophysiology of malignancy; they can promote genetic changes necessary for the initiation, growth, progression of the malignant cell and also can provide resistance to oncological treatments; another point of view claims that a permanent increased level of ROS generates a cytotoxic effect, activating apoptotic pathways or inhibiting the resistance to oncological treatments [4].

CML (chronic myeloid leukaemia) is characterized by the presence of a reciprocal translocation between the long arm of chromosome 9 and the long arm of chromosome 22-t (9; 22) (q34; q11), leading to the formation of a hybrid gene-BCR-ABL-that encodes the synthesis of a protein with a 210 kDa molecular weight, p210-bcr-abl, which has an intense tyrosine kinase activity, transforming hematopoietic stem cells into leukemic cells [5].

Uncontrolled growth of leukemic progenitor cells leads to the manifestation of the disease. It appears that the ectopic expression of BCR-ABL induces an increased production of ROS in hematopoietic cells, via activation of the PI3K/mTOR pathway [6].

First generation (imatinib), second generation (dasatinib, nilotinib, bosutinib) and third generation (ponatinib-for CML presenting T315I mutation) TKIs (tyrosine kinase inhibitors) are the current standard treatment in CML and they frequently induce major molecular response [7].

CML chronic phase cells may acquire additional genetic changes that confer resistance to TKIs, leading to disease progression [8], aspect in which OS is involved [9].

In addition to neoplastic pathology, OS is involved in a number of other chronic pathologies: diabetes mellitus, dyslipidaemia, obesity [10], cardiovascular pathology, chronic kidney disease.

It has been demonstrated that OS is involved in the pathogenesis and evolution of diabetes mellitus, including insulin resistance and related complications [11].

The increase in oxygen and nitrogen free radicals level is related to lipid peroxidation, non-enzymatic protein glycosylation and glucose oxidation, leading to the onset of diabetes and complications' development [12].

Hypercholesterolemia contributes to alteration of the physical properties of the cell membrane, facilitating the mechanisms of ROS generation and their extracellular release. The consequence is membrane lipids peroxidation, generating other free radicals [13].

Through the increased number of mitochondria in cardiovascular tissue, a substantial amount of ROS is formed within the cardiovascular system, which, in physiological conditions are neutralized by the antioxidant systems. A deficient antioxidant defence or specific mitochondrial dysfunction can lead to cardiovascular pathologies based on OS [14].

It has been proved that in patients with chronic kidney disease (CKD) there is an increased level of OS, one of the sources being chronic inflammation. It has been established a correlation between renal dysfunction and inflammatory mediators and markers, such as C reactive protein, interleukin-6, tumoral necrosis factor and fibrinogen, suggesting that CKD is an inflammatory process in itself [15].

In this paper we set out to study the oxidative status (level of ROS, respectively the antioxidant capacity (AC)) of patients with CML, without other associated pathologies, comparing to the oxidative status of patients with CML, associating comorbidities in whose pathophysiology OS is involved (type 2 diabetes mellitus, dyslipidaemia, cardiovascular pathology, CKD).

Materials and Methods

The study included a group of 75 patients diagnosed with CML according to the ELN/WHO criteria, being in the records of the Haematology Clinic of Filantropia Municipal Hospital Craiova (informed consent) and a control group consisting of 20 healthy subjects, free of conditions responsible for the alteration of their redox status. The entire research activity was carried out with the agreement of the Scientific and University Ethics and Deontology Commission of the University of Medicine and Pharmacy of Craiova, according to the notice No. 74/23.02.2017. and according to the patients' rights established by WHO and provided by the Patients' Rights Law no. 46/2003, the Helsinki Declaration revised in 2002 and the General Data Protection Regulation (EU) 2016/679.

The patients in the study group were evaluated hematologically (complete hemoleucogram, hematogenous bone marrow aspirate, cytogenetic examination, BCR-ABL transcript). Additional data about associated comorbidities and specific therapies were obtained from anamnesis, objective examination and study of patients' transcripts. Both CML pacients and control group subjects were determined the level of ROS, respectively the AC in the Laboratory for the assessment of oxidative stress within the University of Medicine and Pharmacy of Craiova.

A FLUOstar Omega microplate reader and a Sigma-Aldrich anti-oxidant kit (CS0790) were used for plasmatic AC determination; meanwhile, a CyFlow SPACE Sysmex flow cytometer including cell sorter function and an Abcam kit for quantitative measurement of cellular ROS (ab113851) were provided for ROS assessment. In addition, an Eppendorf 5702R cooling laboratory centrifuge and an incubator (able to ensure a constant temperature of 37°C for at least 4 hours) were used for the physical processing of blood samples.

Data points had been plotted in Microsoft Excel and statistical analysis of the data was performed in SPSS. Statistical differences between the groups of continuous data have been analysed utilizing a one-way analysis of variance (ANOVA) testing, with Fisher's Least Significant Difference (LSD) post-hoc analysis in order to find the pairs exhibiting the actual differences. Statistical significance, was considered, in all instances for $p<0.05$. All data have been reported as average±standard error of the means (SEM).

Results

The study group included 75 patients diagnosed with CML in treatment with first or second generation TKIs, of which 40 (53.33%) associated comorbidities (type 2 diabetes mellitus (DM), dyslipidaemia (DYS), arterial hypertension (AH), heart failure (HF), CKD)-subgroup 1 and 35 patients (46.66%) without other associated pathologies-subgroup 2.

It should be noted that those with associated pathologies received specific therapies for the comorbidities (oral antidiabetics, angiotensin converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB), diuretics, statins, Nacetylcysteine).

Mean ROS values and mean AC values for subgroup 1, subgroup 2 and control group are provided in Table 1.

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Table 1. ROS and AC in patients with CML and associated comorbidities, CML only and control group (AC-antioxidant capacity, ROS-reactive oxygen species, mM-mmol/L, FI-fluorescence intensity).

Mean value	Subgroup 1	Subgroup 2	Control group
AC (mM)	0,245±0.036	0,198±0.035	0,363±0.037
ROS (FI)	10,412±0.203	10,783±0.258	10,065±0.278

Data analysis revealed a global significant difference between the values of AC for the 3 groups of patients considered, F (2,94)=3.995, p=0.022. The LSD post-hoc analysis revealed a significant difference between subgroup 1 (0,245±0.036mM) and control group (0.363±0.037mM) (p=0.004) and between subgroup 2 (0,198±0.035mM) and control group (0.363±0.037mM) (p=0.048).

There was no global significant difference between the values of ROS for the 3 groups of patients considered, p>0.05, but we noticed that ROS values tended to be higher in patients with CML comparing to the control group.

ROS and AC were evaluated for patients in subgroup 1 with a single associated pathology to CML (DM+CML, AH+CML, DYS+CML, HF+CML, CKD+CML), comparing to subgroup 2 (CML only) and control group.

There was no global significant difference between the values of ROS for the 7 groups of patients considered, p>0.05, but we noticed that ROS values tended to be higher in DM+CML (11.416±1.7 FI) and HF+CML (11.82±0.97 FI), while ROS values tended to be lower in DYS+CML (9.68±0.503 FI) comparing to the control group (10.065±0.278 FI) (Figure 1).

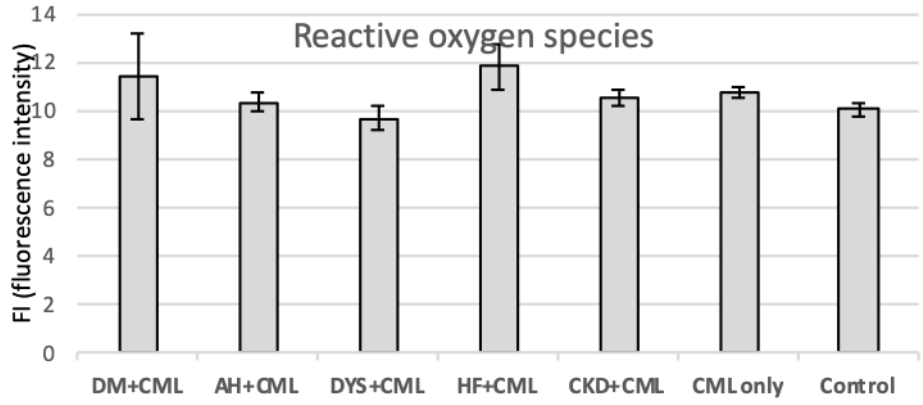

Figure 1. ROS values in patients with CML and one associated pathology.

There was a global significant difference between the values of AC for the 7 groups of patients considered, F (6,79)=2.269, p=0.046. The LSD post-hoc analysis revealed a significant difference between CKD+CML (0.17±0.07mM) and control group (0.363±0.037mM) (p=0.02), and CML only (0.198±0.035mM) and control group (p=0.005) (Figure 2).

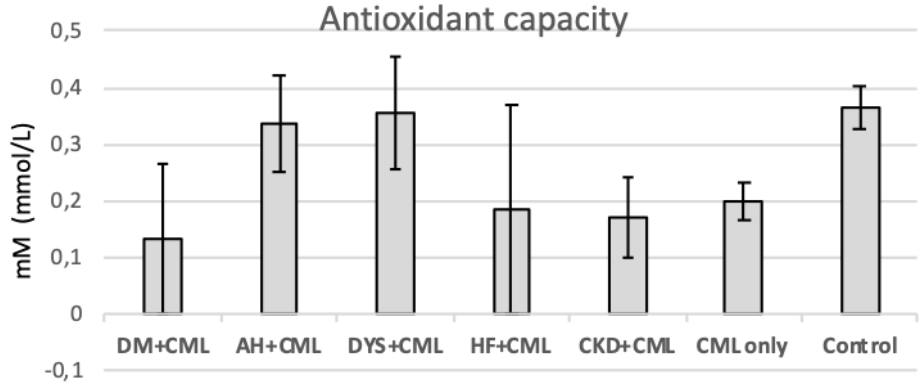

Figure 2. AC values in patients with CML and one associated pathology.

We noted that AC values tend to be lower in DM+CML (0.133±0.133mM) than in the other categories and higher in AH+CML (0.338±0.085mM) and DYS+CML (0.355±0.101mM) comparing to the other categories, except the control group (0.363±0.037mM).

We studied the variability of ROS values in patients with CML associating certain comorbidities (Figure 3).

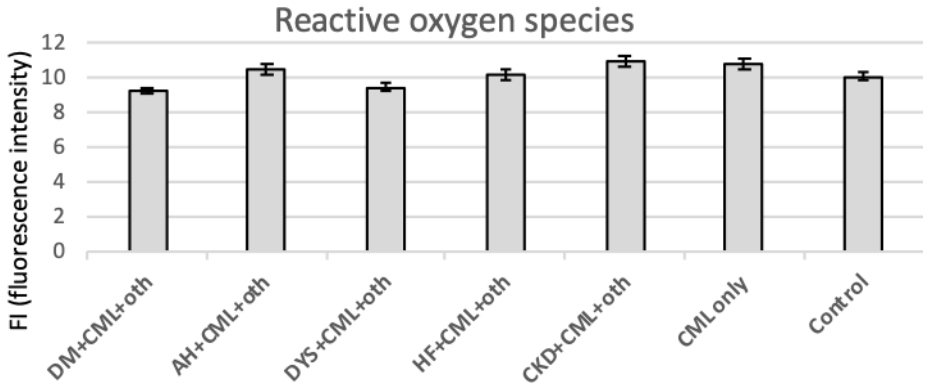

Figure 3. ROS in patients with CML and multiple associated pathologies (oth.-other pathologies).

The LSD post-hoc analysis revealed significant differences between DYS+CML+oth. (9.45±0.261 FI) and CKD+CML+oth. (10.861±0.292 FI) (p=0.047), DM+CML+oth. (9.216±0.108 FI) and CML only (10.783±0.258 FI) (p=0.041), DYS+CML+oth. (9.45±0.261 FI) and CML only (10.783±0.258 FI) (p=0.029), CML only (10.783±0.258 FI) and the control group (10.065±0.278 FI) (p=0.044).

We observed that in DM, DYS and HF, ROS values tend to decrease if patients associate another pathology, besides CML (DM, AH, DYL, HF, CKD) (11,416±1.745 FI-DM+CML, respectively 9.216±0.108 FI-DM+CML+oth., 9.681±0.503 FI-DYS+CML, respectively 9.45±0.261 FI-DYS+CML+oth., 11.82±0.97 FI-HF+CML, respectively 10.125±0.30 FI-HF+CML+oth.).

ROS values tended to increase in patients with AH when they associate other comorbidities (10,372±0.405 FI-AH+CML, respectively 10,455±0.305 FI-AH+CML+oth.) and in patients with CKD with associated comorbidities (10,532±0.337 FI-CKD+CML, respectively 10,861±0.292 FI-CKD +CML+oth.).

We also studied how AC is influenced by the association of different comorbidities (Figure 4).

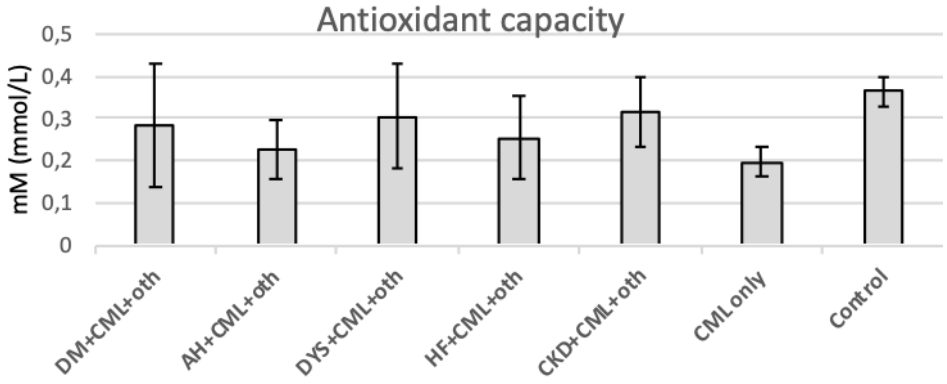

Figure 4. AC in patients with CML and multiple associated pathologies (oth.-other pathologies).

We observed that in diabetic patients, those with HF, as well as those with CKD, AC values tend to increase if they associate another pathology, besides CML (DM, AT, DSL, HF, CKD) (0.133±0.133mM-DM+CML, respectively 0.283±0.146mM-DM+CML+oth., 0.185±0.185mM-HF+CML, respectively 0.255±0.096mM-HF+CML+oth., 0.17±0.071mM-CKD+CML, respectively 0.316±0.081mM-CKD+CML+oth.).

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AC values tended to decrease in hypertensive patients associating other comorbidities (0.338±0.085mM-AH+CML, respectively 0.227±0.07mM-AH+CML+oth.) and in dislipidemic patients associating other comorbidities (0.355±0.101mM-DYS+CML, respectively 0.304±0.124mM-DYS+CML+oth.). The LSD post-hoc analysis revealed a significant difference between CML only (0.198±0.035mM) and control group (p=0.009).

Analysing the oxidative status according to the number of comorbidities associated with CML, there is no global significant difference between ROS values for the 5 groups of patients considered (3 associated pathologies, 2 associated pathologies, one pathology, CML only, control group) (p>0.05). ROS values tended to decrease as the number of associated comorbidities increases (Figure 5).

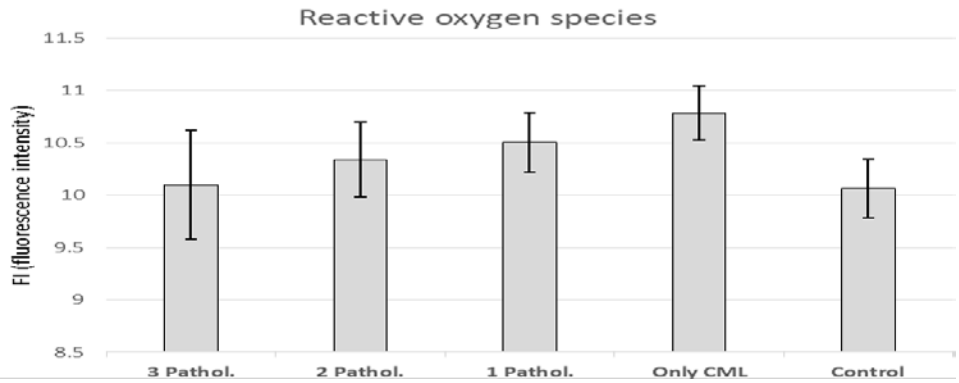

Figure 5. ROS values in patients with CML depending on the number of associated comorbidities.

Regarding the AC, the LSD post-hoc analysis revealed a significant difference between group of patients with two associated pathologies (0.18±0.072mM) and CML only (0.198±0.035mM) (p=0.033), and also between CML only (0.198±0.035mM) and control group (0.363±0.037mM) (p=0.006) (Figure 6).

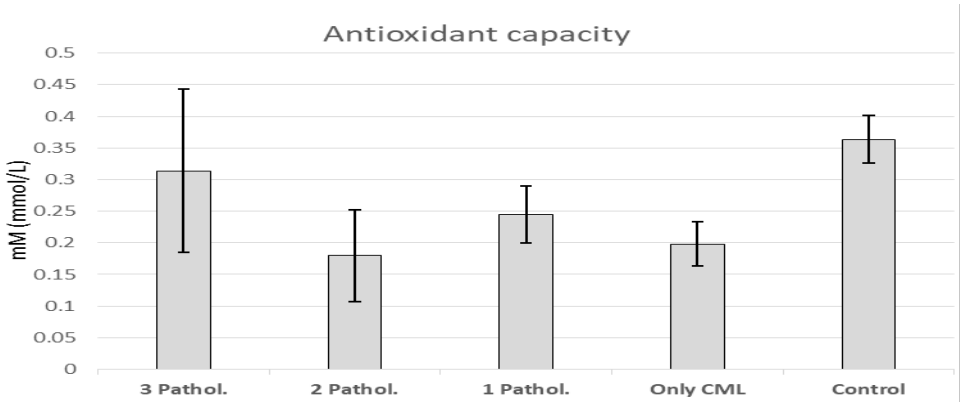

Figure 6. AC values in patients with CML depending on the number of associated comorbidities.

Discussions

In the specialty literature there is evidence about the involvement of OS in the pathophysiology of malignancy and the pharmacokinetics of oncological treatments, some supporting the involvement of ROS in the initiation and progression of the disease, treatment resistance development [16], while others supporting the proapoptotic effect of OS induced by some oncological therapies [17].

In the case of CML, most scientific evidence support the involvement of OS in the onset of the genetic mutation responsible for the BCR-ABL oncogene, as well as the fact that the oncogene is responsible for generating a large amount of ROS, responsible for disease progression, additional mutations and development the treatment resistance [18-20].

In our study, we observed that in patients with CML (regardless of the associated comorbidities) ROS values tend to be

higher than in the control group (10.412±0.203 FI-subgroup 1, 10.783±0.258 FI-subgroup 2 vs. 10.065±0.278 FI-control group), while AC values tends to be lower than in the control group (0.245±0.036mM-subgroup 1, 0.198±0.035mM-subgroup 2 vs. 0.363±0.037mM-control group).

This observation is supported by similar data from the literature that incriminates the involvement of OS in the pathophysiology of CML [18,19].

Analysing the tendency of ROS values, respectively AC values in subgroup 1 and subgroup 2, we observed that in subgroup 1 (CML and other associated pathologies) ROS values tend to be lower while AC values tend to be higher than values in subgroup 2 (CML only) (10,412±0.203 FI-subgroup 1, 10.783±0.258 FI-subgroup 2, respectively 0.245±0.036mM-subgroup 1, 0.198±0.035mM-subgroup 2); this aspect seems contradictory to data from the literature supporting the involvement of OS in all the comorbidities pursued in our study (DM [21], DYS [22], AH, HF [23], CKD [24]).

The explanation would be that, in addition to the standard treatment for CML (TKIs), patients in subgroup 1 also receive specific treatments for the associated pathologies (DM-oral antidiabetics, DYS-statins, AH-ACE/ARB, HF-diuretics, beta-blockers, CKD-Nacetylcysteine, vitamin E) and there are evidence in literature to incriminate these pharmacological classes in modulating systemic level of OS.

We noticed that ROS values tend to be higher in DM+CML and HF+CML comparing to the control group. There is evidence in the literature that support the involvement of ROS in the pathogenesis of DM [25] and HF [26], thus explaining a higher value of ROS in these categories of patients. Surprisingly, diabetic patients had such a high mean ROS value, although they were receiving oral antidiabetics. There are multiple proofs in literature that sustain the capacity of oral antidiabetics to modulate OS by reducing ROS [27] and increasing AC [28,29]. In this case, it could be about a potential drug interaction between antidiabetics and TKIs, aspect that could be studied in a future research activity.

Regarding the association of the therapeutic classes, we specify that in the categories of patients in which ROS values tend to be lower than ROS values in CML only (AH+CML, DYS+CML, CKD+CML), the associated treatments included ACE/ARB, statins, Nacetylcysteine, vitamin E, which are scientifically proved to reduce the rate of ROS production [30-32]. Evidence of reducing ROS levels by administration of diuretics, beta blockers (therapeutic classes in the treatment of HF), is still uncertain, appearing to have rather an effect of increasing the efficiency of antioxidant systems [33].

The fact that ROS values tend to be lower in DYS+CML comparing to the control group is explained by the use of statins, whose effect of inhibiting the pathways of ROS production is documented in several studies [34,35].

Regarding AC, we noted that values tend to be higher in DYS+CML and AH+CML, aspect explained by the additional antioxidant effect provided by the statin therapy in dyslipidaemias [36], and probably secondary to the ACE/BRA treatment in hypertensive patients [30].

Also, we noted that AC values tend to be lower in DM+CML than in the other categories. Correlating this information with the increased ROS value obtained in diabetic patients and, apparently in contradiction with the literature data, which prove that oral antidiabetics reduce ROS and increase AC [37], we raise again the suspicion that there is a possible interaction between TKIs and oral antidiabetics that nullifies the antioxidant effects of specific treatment for DM.

In CKD, we would have expected to obtain an increasing trend of AC values under the conditions of supplementation with antioxidant agents (vitamin E, Nacetylcysteine). In our study, it was obtained a significant difference between CKD+CML (0.17±0.07mM) and control group (0.363±0.037mM), patients with CKD+CML presenting lower AC values than the control group. Most likely, a large part of the antioxidant reserve (exogenous and endogenous) was used to neutralize ROS produced at an increased rate under the conditions of the massive chronic inflammation in CKD. There is scientific evidence of the intense production of ROS in CKD [38,39] and, in addition, their excessive accumulation under conditions of impaired excretory function [40].

It is surprising that in our study, in patients' groups DM+CML, DYS+CML and HF+CML, ROS values tend to decrease if they associate another pathology.

This aspect may suggest that, by associating specific treatments for the comorbidities (ACE/ARB, statins, N acetylcysteine, vitamin E), whose involvement in the oxidative status is supported by several specialized papers [27-36],

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the production of ROS is diminished/the antioxidant systems are potentiated.

Correlating these data with the comparative study of AC values, which were observed to increase in diabetic patients if they associate another pathology besides CML, we tend to consider that the predominant involvement of specific treatments for DM is in modulating antioxidant defence [37].

In patients with CKD, AC values tend to increase if they associate another pathology, besides CML. The explanation would be that beside the antioxidant defence provided by the exogenous supplementation with antioxidants (Nacetylcysteine, vitamin E), there is an additional effect of stimulating the antioxidant systems through the specific therapies for the associated pathologies [38-40].

Analysing AC according to the number of associated pathologies, we observed a significant difference between group of patients with two associated pathologies and group of patients only with CML, which is probably explained by the potentiating effect of associated treatments on antioxidant defence.

ROS values tend to decrease as the number of associated comorbidities to CML increases. This suggests also that the associated treatments have an effect of diminishing the endogenous production of ROS. However, there is the possibility that TKIs therapy have a prooxidative effect in patients with CML, not compensated by a deficient AC in these patients, but compensated by the modulatory effect on the OS of the associated therapies. There is still no clear evidence of TKIs' mechanisms of action involving ROS [41,42].

Conclusions

In conclusion, in the present research activity we found out the involvement of OS in the pathogenesis of CML, considering the higher ROS values and the lower AC values in the patients with CML treated with TKIs (whether or not they associate other pathologies), comparing to the control group.

We found out a decreasing tendency of ROS values and an increasing tendency of AC values in patients with CML when they associate other pathologies and receive specific treatments for the comorbidities; this aspect is, most probably, the effect of the associated treatment in modulating the oxidative status.

Analysed separately, however, it appears that DM and HF, as associated comorbidities to CML, are characterized by an oxidative status dominated by ROS production and a significant reduction of AC, despite the specific associated therapies.

In this situation, it could be about possible drugs interactions between standard CML treatment and antidiabetic therapy, respectively HF therapy. This aspect could be studied in a future research activity, which will include, also, the effect of these drugs interactions on the prognosis of CML patients following TKIs therapy.

Conflict of interests

None to declare.

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