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Original scientific paper

Effect of standardized *Aronia Melanocarpa* extract on oxidative stress and antioxidant status in patient with cronic myeloid leukemia treated with imatinib

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Abstract

Antioxidant status in patients with chronic myeloid leukemia (CML) is significantly decreased in comparison with healthy individuals. Oxidative stress (OS) may be associated with the pathophysiology of CML and can influence on development of resistance to imatinib.

The aim of our study was to investigate the effect of *Aronia melanoc*arpa extract (A-lixir 400 PROTECT®) on OS in CML patients treated with imatinib.

In this study a total of 40 CML patients treated with imatinib for longer than 1 month were included: twenty patients were treated with imatinib and A-Lixir 400 PROTECT® (treatment group) and twenty patients were treated only with imatinib (control group). OS parameters (d-ROM, PAT and OSI) were measured at the initial visit, and after 21 and 42 days of treatment. Adjuvant treatment with A-Lixir 400 PROTECT® could lead to attenuation of OS. d-ROM and OSI in this group of patients were significantly higher at initial visit when compared to values after 21 and 42 days of treatment ($p<0.05$). Total antioxidant capacity (PAT) was significantly higher after 21 and 42 days of treatment initiation in comparison with the pretreatment values. In the control group no significant differences were obtained between investigated parameters at any time of measurement. We can conclude that adjuvant treatment with A-Lixir 400 PROTECT® after 21 and 42 days lead to significant reduction of OS in patients with CML treated with imatinib.

Key words: Oxidative stress, d-ROM, PAT, OSI, chronic myeloid leukemia, imatinib, *Aronia melanocarpa*

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by uncontrolled proliferation of myeloid cells in the bone marrow and in the peripheral blood without the loss of their capacity to differentiate. The distinctive cytogenetic abnormality in CML and the hallmark of the disease is the presence of Philadelphia (Ph.) chromosome caused by

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reciprocal translocation t (9; 22) (q34; q11) with fusion of BCR and ABL1 genes into the pathogenic BCR-ABL1 oncogene (Gao et al., 2009; Udensi et al., 2014). The BCR-ABL1 oncogene is responsible for constitutive activation of the tyrosine kinase pathway that leads to uncontrolled proliferation of mutant hematopoietic stem cells (HSCs) in comparison to normal HSCs with consecutive gradual displacement of normal HSCs.

The clinical signs of chronic myeloid leukemia (CML) develop gradually and evolve as the disease advances through its three stages: chronic, accelerated, and blast with most of the patients being diagnosed in the chronic phase. Symptoms of CML vary widely, ranging from no apparent symptoms to those arising from overt leukostasis, which is more prevalent in the blast phase. However, hyperleukocytosis is a common feature observed in virtually all patients across all phases of the disease. Other symptoms may include splenomegaly and constitutional symptoms such as weight loss, fatigue, malaise, fever of unknown origin, and early satiety. Hence, consideration of a diagnosis of CML is warranted when a patient exhibits leukocytosis, along with either a normal or slightly elevated platelet count, a peripheral blood smear revealing immature granulocytes, eosinophilia, basophilia, and evidence of splenomegaly. For final diagnosis of CML, the demonstration of the BCR-ABL1 gene rearrangement is essential. Studies investigating oxidative stress markers in CML patients have revealed significant findings, specifically, notable elevation of well-known oxidative stress markers levels such as plasma malondialdehyde and protein carbonyls ($p<0.05$) compared to healthy volunteers (Ahmad et al., 2008). Additionally, antioxidant status was significantly decreased in CML patients when compared to healthy participants. These findings strongly suggest an association between oxidative stress and the pathophysiology of chronic myeloid leukemia. Such insights not only enhance our understanding of CML but also open avenues for exploring potential therapeutic interventions targeting oxidative stress pathways to improve patient outcomes.

The introduction of tyrosine kinase inhibitors (TKIs) dramatically changed the therapeutic landscape of CML in the last two decades, with life expectancy now being very close to that of age matched individuals in the general population (National Cancer Institute, 2024).

In CML, TKIs work by inhibition of the function of the abnormal BCR-ABL1 protein responsible for uncontrolled myeloproliferation, resulting in CML cells apoptosis. Imatinib mesylate was the first protein-tyrosine kinase inhibitor with the capacity to block the constitutive action of BCR-ABL1 protein causing subsequent downstream apoptosis without further cell differentiation.

Despite the fact that imatinib is the current gold standard for newly diagnosed adult and pediatric CML patients in chronic phase, there is a rising concern regarding primary or acquired drug resistance. Many studies have investigated the involvement of oxidative stress (OS) not only in the CML pathogenesis but also its contribution in the development of drug resistance. Although the involvement of OS in the CML pathogenesis is already acknowledged, there are numerous additional factors (comorbidities, additional therapies) that can modulate the OS and maybe affect the evolution and prognosis of this disease.

Recent papers have shown the potential benefits of concomitant use of antioxidants and TKIs in CML patients in an attempt to reduce OS.

Aronia melanocarpa (*A. melanocarpa*) or black chokeberry is a fruit/plant which belongs to the *Rosaceae* family and is native to North America (Milosavljevic et al., 2021; Ren et al., 2022). However, it has been commonly used in Europe as ingredient for juices, wine, jams, teas and cordial liqueurs (Milosavljevic et al., 2021; Ren et al., 2022; Sidor et al., 2019; Yang et al., 2021). Among numerous plant foods, berry fruits are known to have the greatest antioxidant potential due to the large amount of polyphenols (Milosavljevic et al., 2021; Van Hung, 2016). Chokeberry (*Aronia melanocarpa*) has a significantly higher content of polyphenols, such as anthocyanins, flavonols, proanthocyanidins, and phenolic acids, and consequently higher antioxidant activity than other berries (Ovaskainen et al., 2008; Skupien et al., 2005). Previous studies showed that chokeberry fruit and extracts exert extensive beneficial effects in chronic diseases, especially in diseases connected with oxidative stress (Jankowski et al., 2000; Jurikova et al., 2017; Milosavljevic et al., 2021; Minato et al., 2003; Ren et al., 2022). Recent researches have focused their attention on *A. melanocarpa* due to its numerous health benefits in a broad range of pathological conditions. It has been reported that *A. melanocarpa* exhibits substantial gastroprotective, hepatoprotective, antiinflammatory and antiproliferative activity (Milosavljevic et al., 2021; Thi Nhuan et al., 2018). Furthermore, other health-promoting effects of plant extracts involve antiatherosclerotic, antiplatelet, hypoglycemic properties, and may also reduce systolic and diastolic pressure.

A-Lixir 400 PROTECT® is a product that contains 400 mg of polyphenols from a standardized extract of the *A.melanocarpa* plant in 30 ml of solution. The composition and representation of polyphenolic compounds in fresh fruit, with and extract of aronia is similar, but differs in the content and concentration of polyphenols. The extract is the best source of bioavailable polyphenolic compounds with strong antioxidant properties (Denev, 2012). The amount of polyphenols in 30 mL of A-Lixir 400 PROTECT® solution corresponds to the daily intake requirements for these compounds in the body. The problems arise because only 7 to 15% of the daily requirements for these compounds are ingested with the usual diet. Also, the fact that despite a sufficient intake of fresh fruits and vegetables, the resorption is not sufficient due to the impossibility of their sufficient digestion, which is why they are expelled through the feces, can also be a

Table 1. Qualitative and quantitative composition of polyphenols in A-Lixir 400 PROTECT®

A-Lixir 400 PROTECT® composition of polyphenols	polyphenols (mg) in 30 ml extract
FLAVONOIDS (total)	16.03
Rutin	3.55
Hyperoside	8.12
Isoqarcetin	4.36
ANTOCYANS (total)	109.29
Cyanidine-3-galactoside	80.40
Cyanidine-3-glucoside	4.92
Cyanidine-3-arabinoside	19.71
Cyanidine-3-xyloside	4.26

problem (Burton-Freeman et al., 2019).

Table 1 shows the qualitative and quantitative composition of polyphenols in A-Lixir 400 PROTECT®.

In order to further clarify these observations, we evaluated and compared the oxidative stress parameters in CML patients treated with imatinib only and CML patients treated with imatinib plus A-Lixir 400 PROTECT®.

Material and methods

Patients

This open-label, controlled study carried out from June 2022 to December 2023 and included 40 patients (male and female) with chronic myeloid leukemia treated with imatinib. The patients were diagnosed at University Clinic of Hematology, Medical faculty, Ss. Cyril and Methodius University in Skopje, R.N. Macedonia using WHO 2017 diagnostic criteria for CML. The inclusion criteria were: CML patients ≥ 18 years old that underwent treatment with imatinib for longer than one month, and who at the time of inclusion were not receiving other antioxidants as adjuvant treatment.

The exclusion criteria from the study were CML patients with positive history of an allergic reaction to pollen and/or to any of the components of the product intended to be used; positive history of continuous use for at least 30 days of chokeberry extract or another strong antioxidant in the previous three months; patients with clinically significant immunodeficiency conditions (organ transplantation, use of immunosuppressive drugs, etc.); patients with clinically significant liver or kidney disease; patients with a history of drug and/or alcohol abuse in the past 12 months; participation in other clinical studies in the past two months.

In this study 20 patients (male and female) were enrolled in the group treated with imatinib and A-Lixir 400 PROTECT® in the dose of 30 mL/day during 42 days. The other control group of included 20 patients treated only with imatinib. Medical doctors included in the study were in regular contact with the patients in order to check on any health changes between the hospital visits and to confirm the regular intake of the products.

Ethical approval

The research was conducted with respect to the Helsinki Declaration on Medical Research and after approval of the Ethics Committee of the Medical faculty, Ss. Cyril and Methodius University in Skopje, R.N. Macedonia, and all of the included patients signed a consent form at the entry of the study.

Treatment and study products

In this study 20 patients (male and female) were enrolled in the group treated with imatinib and A-Lixir 400 PROTECT® in the dose of 30 mL/day during 42 days. A-Lixir 400 PROTECT® is standardized *A. melanocarpa* extract and an official product of the pharmaceutical company Pharmanova (Belgrade, Serbia). This product contains 400 mg/30mL of polyphenols, and the recommended daily dosage is 30 mL.

The other group of 20 patients was control and was treated with imatinib only.

During the study, patients from both group had three clinical examinations by the investigators (screening at initial visit and after 21 and 42 days of treatment).

At each visit, anamnestic data was taken from each patient included in the study, a physical examination was performed, and blood sample was taken for laboratory analyzes (10 mL) and to determine the parameters of oxidative stress (5 mL).

Methods for determination of oxidative stress parameters

PAT (total antioxidant power, iron reducing) and d-ROMs (plasma peroxides) were measured on a FRAS5 analytical photometric system (H&D, Italy) (Alberti et al.,2000; Carratelli et al., 2006). The instructions of the

Table 2. Demographic characteristics of the patients

Characteristics	Control group (Imatinib) ± SD	Treatment group (A-Lixir 400 PROTECT® and imatinib) ± SD
Age (years)	54.35±16.71	55.35±7.15
Height (cm)	173.25±5.39	172.65±5.67
Weight (kg)	74.85±9.54	74.40±5.78
BMI	24.86±2.20	24.97±1.67

manufacturer were followed for the both tests. All samples were stored frozen in an upright position in freezers at the Institute of preclinical and clinical pharmacology and toxicology at a temperature -80 ± 10 ºC until analyzed. The procedure was done according to the producers' guidelines for the both, d-ROMs and PAT tests. Three samples (on admission and after 21 and 42 days of treatment) were collected and analyzed.

The d-ROMs and PAT are reported in equivalents of H202 and ascorbic acid, respectively. The d-ROMs and PAT reference normal values are 250–300 U. Carr (1 U. Carr = 0.08 mg H202/dL) and 2200–2800 U. Carr, respectively. Oxidative stress index (OSI) presents information obtained from d-ROMs fast test and the PAT test that is automatically calculated by the dedicated spectrophotometer FRAS5 with normal reference values less than 40 given by the manufacturer (H&D srl, 43124 Parma, Italy).

Statistical analyses

Data was described as number and/or percentage, or mean and standard deviation (SD) or standard error of mean (SEM), where appropriate. Differences between groups were explored using the t-test. A p-value less than 0.05 was considered significant. All analyses were made using the statistical program.

Table 3. Laboratory parameters of control and treatment group

Parameters	Control group			Group treated with A-Lixir 400 PROTECT®		
	Initial visit	21 days	42 days	Initial visit	21 days	42 days
Hb (g/L)	134.9±13.18	132.6±9.57	135.15±8.77	131.6±12.60	131.2±10.29	134.05±9.99
Le (x 10^9L)	13.98±24.74	10.05±10.29	8.8±5.38	10.96±14.17	9.06±7.31	10.76±6.76
Tr (x1000/µL)	221.6±80.93	213.7±80.99	224.15±85.81	217.15±86.02	219.6±92.6	211.15±78.93
Glucose (mmol/L)	5.71±0.95	5.60±0.99	4.75±1.37	5.53±0.83	5.63±0.62	5.45±0.49
Urea (mmol/L)	4.75±1.37	5.55±1.18	5.27±0.99	5.28±2.20	5.31±1.68	5.55±1.77
Creatinine (µmol/L)	85.6±12.69	85.3±9.81	83.25±8.66	96.7±14.8	89.4±15.35	92.05±14.99
AST (U/L)	23.75±7.35	26.05±6.50	25.55±5.09	27.3±5.57	29.3±5.05	27.4±4.50
ALT (IU/L)	28.75±14.30	29.95±13.12	26.75±7.28	28.55±7.92	27.8±7.60	32.7±9.31
LDH (U/L)	421.9±232.31	366.16±92.57	330.8±83.43	516.1±278.94	469.35±150.92	366.55±97.58
Protein total (g/L)	73.1±6.41	73.25±6.83	73.65±6.49	71.3±6.41	72.8±7.61	72.35±7.21
Albumin (g/L)	43±3.40	40.85±3.33	41.25±2.77	41.7±6.42	40.3±4.76	38.85±3.41
Bilirubin total (µmol/L)	10.57±4.27	10.8±3.49	10.45±3.35	11.1±3.78	10.63±3.57	9.97±3.45
Cholesterol (mmol/L)	4.52±0.85	4.61±0.80	4.51±0.71	4.34±0.81	4.36±0.71	4.37±0.78

Results

Demographic characteristics and laboratory findings

In our study 40 patients with chronic myeloid leukemia were included; 20 in the control group were treated only with imatinib and 20 were treated with imatinib plus A-Lixir 400 PROTECT® for 42 days. In the control group 10 were female (50%) and 10 were male (50%), and in the treated group with imatinib plus A-Lixir 400 PROTECT®, 7 were female (35%) and 13 were male (65%) (Table 2).

The laboratory values of the control group at their initial visit were comparable with the treatment group. There was not significant difference in laboratory parameters between control group and treatment group after twenty-one (21) and forty-two (42) days of treatment. Also, no significant difference was shown between laboratory parameters in control and treatment group obtained at the initial visit at day 21 and at day 42 of treatment. The mean values of some laboratory parameters are presented in Table 3.

There was not statistically significant difference between hematological and biochemical analyses in the control group and treatment group while comparing pre-treatment values and post- treatment values.

Effect of treatment with A-Lixir 400 PROTECT® on oxidative stress markers

The results from our study suggest that adjuvant treatment with *Aronia melanocarpa* extract (A-Lixir 400 PROTECT®) could lead to attenuation or even significant reduction of oxidative stress. The results presented in Table 4 show that the parameters of the oxidative stress d-ROM, PAT and OSI index in the control group and treatment group before treatment and after 21 and 42 day treatment.

The results presented in Table 4 show that the parameters of the oxidative stress d-ROM and OSI in the treatment group were higher before treatment when compared to the post treatment values after 21 days (8.5% for d-ROM and 15.1% for OSI) and 42 days of treatment (15.6% for d-ROM and 23.6% for OSI). For d-ROM, the difference was statistically significant between values obtained before treatment and 42 days of treatment (*p=0.0121*) and for OSI the difference was statistically significant between values obtained before treatment and 42 days of treatment (*p=0.0105*). Parameters of the oxidative stress PAT was higher after 21 days (6.8%) and 42 days treatment (20.6%). For PAT the difference was statistically significant between values obtained before treatment and 21 days (*p=0.0411*) and 42 days of treatment (*p=0.0008*).

No statistically significant difference was found between parameters of the oxidative stress d-ROM, PAT and OSI in the control group when compared pretreatment values and post treatment values after 21 (for d-ROM, *p=0.0046* - statistically significant higher, for PAT, *p=0.4264* and for OSI, *p=0.0958*) and after 42 days treatment (for d-ROM, *p=0.2124*, for PAT=0.1544 and for OSI, *p=0.0636*).

Statistically significant difference was found between parameters of the oxidative stress (d-ROM, PAT and OSI) in control and treatment group when compared post-treatment values after 42 days of treatment (for d-ROM, *p=0.0133*, for PAT=0.0119, and for OSI, *p=0.00007*. After 21 day of treatment, results revealed statistically significant difference between parameters of the oxidative stress d-ROM, *p=0.0435* and OSI, *p=0.0063*. The difference between control and treatment group for PAT was not statistically significant after 21 days of treatment (*p=0.3181*).

Table 4. Mean oxidative markers in patients with chronic myeloid leukemia treated with imatinib (control group) and in group treated with imatinib plus A-Lixir 400 PROTECT® (treatment group)

Parameters	Initial visit±SD	After 21 days	After 42 days
		d-ROM (U.Carr)±SD	
control group	343.85±66.22	365.4±74.70	351.8±73.93
treatment group	336±101.18	307.30±99.52	283.65±91.21
		PAT (U.Carr)±SD	
control group	2646.25±708.24	2614.40±663.39	2590±663.69
treatment group	2653.20±666.15	2834.45±711.36	3200.65±793.9
		OSI±SD	
control group	74.85±20.82	79.90±22.39	82.20±23.72
treatment group	63.05±28.48	53.55±34.10	48.15±24.41

Discussion

The literature highlights the involvement of oxidative stress in the pathophysiology of CML, it's influence in the disease initiation and progression, as well as in the development of resistance to imatinib therapy. Some oncological treatments induce a proapoptotic effect through oxidative stress. In CML, oxidative stress plays a role in initiating the genetic mutation responsible for the BCR-ABL1 oncogene formation. Imatinib is a synthetic tyrosine kinase inhibitor used in the treatment of chronic myeloid leukemia. Various mechanisms of imatinib resistance have been identified, including BCR-ABL11 gene over expression, BCR-ABL11 kinase mutations, and genetic variation and/or altered expression of imatinib genetic transporters. Among them, reactivation of the BCR-ABL11 protein by mutations in the kinase domain, such as the T315I mutation, has been documented as one of the most prevalent mechanisms leading to imatinib resistance (Ahmad et al., 2010; Labachevski et al., 2023; Sailaja et al., 2010). Research in recent years has attributed a greater role in the development of resistance to imatinib to oxidative stress. The impact of oxidative stress in patients with chronic myeloid leukemia is still unclear and more profound investigations are necessary. Previous studies have shown that the transformation of the BCR-ABL11 oncogene can be induced by the increased generation of reactive oxidative compounds and subsequent redox imbalance. It is well known that excessive production of reactive oxidative compounds such as superoxide radicals (O_2^-), hydrogen peroxide (H_2O_2) and highly reactive hydroxyl radicals (OH^-) leads to oxidative damage to lipids, proteins and DNA. If not corrected, DNA damage can lead to mutagenesis and cause the initiation or development of various types of malignant tumors.

In our study we demonstrated that standardized *A.melanocarpa* extract (A-Lixir 400 PROTECT®) showed significant alleviation of markers of oxidative stress (d-ROM, PAT and OSI) during forty-two days treatment in patient with chronic myeloid leukemia treated with imatinib longer than 1 month. Results from our previous study confirm that patients with CML treated with imatinib have a significantly higher level of oxidative stress compared to healthy subjects as measured by markers of oxidative stress, d-ROM and oxidative stress index (OSI) (Labachevski et al., 2023).

Currently there are large number of data that prove the antioxidant effect of A. melanocarpa and the polyphenols found in its composition (Milosavljevic at al., 2021; Sidor et al., 2019; Thi et al., 2018; Yang et al., 2021). Aronia extract inhibits the enzyme 15-lipoxygenase and xanthine oxidase which are peroxidative and prooxidative enzymes and increase the production of reactive oxygen radicals (ROS). The antioxidant properties of A. melanocarpa have also been confirmed in clinical studies performed in healthy volunteers who received chokeberry juice or chokeberry ethanol extract for several weeks (Istas et al., 2019; Sweeney et al., 2022). Some clinical trials indicated that consumption of Aronia berries may not have sufficient antioxidant activities measured by the biomarkers of oxidative stress and the total antioxidant activity in plasma and urine (Puuponen-Pimia et al., 2013).

Results from our study showed that daily consumption of standardized extract of *A. melanocarpa* (A-Lixir 400 PROTECT®) is effective in reducing the oxidative stress in CML patients treated with TKI longer than 1 month. The role of oxidative stress in the development of resistance to imatinib becomes relevant in studies published recently (Ammar et al., 2020; Ciarcia et al., 2015; Gajski et al., 2019; Glowacki et al., 2021; Teppo et al., 2017). A significant disturbance of the oxidative status has been determined in CML patients treated with imatinib, both in cases that have not developed resistance to imatinib, and in patients that have acquired resistance to the drug. In relation to a healthy population, changes were observed in the values of the parameters that determine the oxidative status of the organism: concentration of malondialdehyde (MDA), catalase activity (CAT), superoxide dismutase activity (SOD), glutathione peroxidase activity (GPx), concentration of reduced glutathione (GSH) and vitamin C. In these patients, significantly higher values of malondialdehyde and catalase activity and reduced values for the activity of superoxide dismutase, glutathione peroxidase, concentration of reduced glutathione and vitamin C were detected. Additionally, significant differences in oxidative status between patients who were resistant and the group of patients who did not develop resistance to imatinib were found. In the group of patients resistant to imatinib there were significantly higher values of malondialdehyde (MDA), and increased activity of catalase (CAT) and superoxide dismutase (SOD). However, the conclusion from these studies was that additional investigations are needed, but with increasing evidence that the development of resistance to imatinib was associated with oxidative stress.

Conclusion

In summary, our results are in line with previous studies demonstrating that standardized extract of *A. melanocarpa* (A-Lixir 400 PROTECT®) given at dose of 30 ml during 21 and 42 days significantly reduced oxidative stress parameters (d-ROM, PAT and OSI) in CML patients treated with imatinib. The noteworthiness of oxidative stress in the development of imatinib resistance has become increasingly recognized. Further studies with a longer duration and a larger number of patients are needed to emphasize the importance of reducing oxidative stress in CML patients.

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Резиме

Ефект на стандардизиран екстракт од Aronia Melanocarpa врз оксидативниот стрес и антиоксидативниот статус кај пациенти со хронична миелоидна леукемија третирани со иматиниб

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Клучни зборови: оксидативен стрес, d-ROM, PAT, OSI, хронична миелодна леукемија, иматиниб, *Aronia melanocarpa*

Антиоксидантниот статус кај пациентите со хронична миелоидна леукемија (ХМЛ) е значајно намален кај пациентите со ХМЛ во споредба со здрави испитаници. Оксидативниот стрес (ОС) може да биде поврзан со патофизиологијата на ХМЛ и развојот на резистенција кон иматиниб.

Целта на нашата студија беше да се испита ефектот на екстракт од *Aronia melanocarpa* (A-lixir 400 PROTECT®) врз ОС кај пациенти со ХМЛ третирани со иматиниб.

Во оваа студија беа вклучени вкупно 40 пациенти со ХМЛ кои беа третирани со иматиниб подолго од 1 месец: дваесет пациенти беа третирани со иматиниб и A-Lixir 400 PROTECT® (испитувана група) и дваесет пациенти кои беа третирани само со иматиниб (контролна група). Параметрите на ОС (d-ROM, PAT и OSI) беа мерени при првата посета и по 21 и 42 дена третман.

Адјувантен третман со A-Lixir 400 PROTECT® доведува до намалување на ОС. d-ROM и OSI во оваа група беа сигнификантно поголеми пред почеток на третманот во однос на вредностите добиени по 21 и 42 дена третман ($p<0.05$). Вкупниот антиоксидантен капацитет (PAT) имаше сигнификантно поголеми вредности по 21 и 42 дена третман во однос на вредностите добиени пред почеток на третманот. Во контролната група не беа забележани сигнификантни разлики помеѓу испитуваните параметри добиени во различните временски точки на мерење.

Заклучок од оваа студија е дека адјувантен третман со A-Lixir 400 PROTECT® по 21 и 42 дена доведува до значајно намалување на ОС кај пациенти со ХМЛ третирани со иматиниб..