IMPROVED CLINICAL PRACTICE AND UPDATED MANAGEMENT IN CHRONIC MYELOID LEUKEMIA

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Rezumat. Practica clinică perfecţionată şi managementul actualizat în leucemia mieloidă cronică

Leucemia mieloidă cronică (LMC) constituie un proces neoplazic clonal al sistemului hematopoietic, care rezultă din transformarea malignă a celulei stem, cu menţinerea capacităţii de diferenţiere către toate liniile celulare. În studiu sunt înrolaţi 125 bolnavi cu diferite faze ale LMC, în vârsta cuprinsă între 19 – 81 ani (media de vârstă – 46,1 ± 2,13 ani), aflaţi la evidenţă şi tratament în IMSP Institutul Oncologic în perioada anilor 2005 – 2013. Diagnosticul a fost stabilit în faza cronică tardivă în 113 (90,4 ± 2,32%) cazuri, în faza de accelerare şi acută – în 12 (9,6 ± 2,02%) cazuri. Determinarea concomitentă a Ph cromozomului, genei de fuziune BCR/ABL cu proteinele himerice p210 / p190 este de importanţă practică majoră atât pentru diagnosticarea LMC, cât şi pentru evaluarea adecvată a răspunsului la tratament. Analiza discriminantă a relevat coeficienţii mai înalţi de corelaţie canonică la următorii factori de depistare tardivă: debutul asimptomatic sau oligosimptomatic al bolii (0,548), educaţia sanitară joasă a populaţiei (0,525) şi debutul cu simptomatologia clinică indiscretă, cu simptoame paraneoplazice (0,340). Imatinib mesylate şi dasatinib constituie tratament de elecţie în faza cronică şi de accelerare a LMC, fiind net superioară în raport cu chimioterapie convenţională şi interferon-α prin posibilitatea atingerii remisiunii hematologice complete, remisiunii citogenetice complete şi ameliorării calităţii vieţii pacienţilor. Indicele supravieţuirii generale în sublotul investigaţional afiliat de GIPAP peste 3 ani a constituit 66%, fiind net superior ($p < 0,05$) în raport cu sublotul investigaţional de pacienţi trataţi cu chimioterapie convenţională şi interferon-α (44.5%). Înrolarea în GIPAP şi efectuarea medicaţiei cu imatinib mesylate a favorizat considerabil rezultatele nemijlocite şi la distanţă ale tratamentului, contribuind la reabilitarea fizică a pacienţilor, continuarea sau reluarea activităţilor profesionale la cei plasaţi în câmpul muncii şi reintegrarea lor socială.

Cuvinte-cheie: leucemia mieloidă cronică, factorii de depistare tardivă, imatinib mesylate, dasatinib, remisiunea hematologică completă, remisiunea citogenetică completă, reabilitarea fizică, reintegrarea socială

Summary. Improved clinical practice and updated management in chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a clonal myeloproliferative tumor of hematopoietic system resulting from the stem cell malignant transformation, with maintenance of ability of differentiation of all cell lineages. The study enrolled 125 patients with different phases of CML and age range of 19 - 81 years old (median age - 46.1 ± 2.13 years), who had been treated and followed up at the MSPI Institute of Oncology in 2005 - 2013. The combined screening for Ph chromosome and BCR-ABL p210 and p190 chimeric gene transcripts is mandatory for diagnosis in patients fairly suspected for chronic myelogenous leukemia, as well as for the proper evaluation of the response to treatment. The discriminant analysis revealed the higher coefficients of canonical correlation for the following late diagnosis factors: asymptomatic or oligosimptomatic onset of the disease (0.548), low level of the sanitary education of population (0.525) and the onset with indiscrete clinical and paraneoplastic symptoms (0.340). Imatinib mesylate and dasatinib constitute the first-line therapeutic option in the chronic and accelerated phases of CML, being superior to conventional chemotherapy and interferon-α due to the possibility of the achievement of the complete hematologic response, complete cytogenetic response and the improvement of the patients life quality. The overall 3-year survival rate in patients approved for GIPAP (66.0%) was superior ($p<0.05$) to that achieved after conventional chemotherapy and interferon-α (44.5%). The enrollment of CML patients in GIPAP has considerably favored the short- and long-term results of treatment, contributing to their physical recovery, restoration of the ability to work and social reintegration.

Key words: chronic myeloid leukemia, late diagnosis factors, imatinib mesylate, dasatinib, complete hematologic response, complete cytogenetic response, physical recovery, social reintegration

Резюме. Усовершенствованная клиническая практика и современный менеджмент при хроническом миелолейкозе

Хронический миелолейкоз (ХМЛ), представляет собой клональный опухолевый процесс системы гемопоэза, который возникает в результате злокачественной трансформации стволовой клетки, с сохранением способности дифференцировки по всем клеточным линиям. В исследование включены 125 пациентов с ХМЛ в возрасте от 19 до 81 года (медиана возраста – 46.1 ± 2.13 лет), которые находились на учёте и лечении в ПМСУ Онкологический Институт с 2005 по 2013 гг. Комбинированное исследование на Ph хромосому и транскрипты p210 / p190 химерного гена BCR/ABL является важным с практической точки зрения не только для диагностики ХМЛ, но и для адекватной оценки результатов лечения. Дискриминантный анализ выявил более высокие коэффициенты канонической корреляции для следующих факторов поздней диагностики: асимптоматическое или олигосимптоматическое начало заболевания (0,548), низкий уровень санитарной грамотности насления (0,525) и нехарактерное начало болезни с паранеопластическими симптомами (0,340). Иматиниб мезилат и дазатиниб являются терапией выбора в хронической фазе и фазе акселерации, превосходя конвенциональную химиотерапию и α-интерферон по возможности достижения быстрого и полного гематологического ответа, полного цитогенетического ответа, значительного улучшения качества и увеличения продолжительности жизни больных. В группе пациентов, включенных в GIPAP, показатель 3-летней выживаемости составил 66% и превзошёл таковой ($p<0,05$) у пациентов пролеченных конвенциональной химиотерапией и α-интерфероном (44,5%). Участие пациентов с ХМЛ в программе GIPAP значительно улучшило непосредственные и отдалённые результаты лечения, способствуя их физической реабилитации, восстановлению трудоспособности и социальной реинтеграции.

Ключевые слова: хронический миелолейкоз, факторы поздней диагностики, иматиниб мезилат, дазатиниб, полный гематологический ответ, полный цитогенетический ответ, физическая реабилитация, социальная реинтеграция

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative tumor resulting from the stem cell neoplastic transformation caused by a translocation between the long arms of chromosomes 9 and 22 [1,2,3,4,5,6,16,21,22]. Being monoclonal, the disease may involve myeloid, monocytic, erythroid, megakaryocytic, and B-cell lymphoid lineages. Bone marrow stromal cells aren't affected. The annual incidence of CML ranges between 0.8 – 1.6 cases per 100.000 population. The disease accounts 15 – 20% of all leukemias in adults [1,2,3,4,10,16,22]. This myeloproliferative malignancy occurs mostly in a workable population, with the median age of 40 – 50 years old. Male : female ratio may reach 1.4 : 1. CML involves 2% of childhood leukemias, being most common in the 10 – 14 – year-old age group [16]. A higher incidence of CML is registered among persons heavily exposed to radiation, including survivors of the atomic bomb blasts in Japan and patients undergoing radiotherapy [2,16]. The tyrosine-kinase activity and BCR functional domains of the p210 chimeric protein act on a number of signaling pathways and promote leukemogenesis by changing proliferation, apoptosis, and altered interaction with the cellular matrix. The clinical and hematologic patterns of CML include splenomegaly, myeloid hyperplasia of the bone marrow and hypercatabolic symptoms. The clinical course of the disease consists of 3 consecutive phases: chronic, accelerated and acute, and may be associated with life-threatening emergencies, especially thrombotic and infectious complications, splenic infarcts, bleeding etc. [3,4,8,9,12,13,16]. The CML patients with very high leukocyte counts may have manifestations of hyperviscosity, including priapism, tinnitus, stupor, visual changes from retinal hemorrhages, and cerebrovascular accidents [3,4,5].

The current treatment options in CML include chemotherapy, interferon-α and bone marrow transplantation [1,2,3,4,5,6,7,10,13,14,16,20,21]. In CML conventional chemotherapy doesn't reduce markedly Ph chromosome-bearing cells, therefore transformation to the acute phase is unchanged. Therapeutic decision-making for patients with CML has become more challenging with the advent of imatinib mesylate (Glivec®) – the small molecule tyrosine-kinase inhibitor which blocks the production of the abnormal protein BCR-ABL, that causes the irregular proliferation of myeloid cells [2,3,6,7,11]. Glivec® was approved by the FDA in 2001 and considered as a promising targeted therapy for CML. Glivec® International Patient Assistance Program (GIPAP) is one of the most generous and far-reaching patient assistance programs ever developed for cancer therapy, axed on providing the treatment with imatinib mesylate in different malignant neoplasms [7,10,11,15]. Imatinib mesylate has demonstrated significant activity in patients with all phases of CML, whether they received prior therapy or not, leading to the highest clinico-hematological and cytogenetic response in chronic phase [1,3,4,5,6,7,14]. Nevertheless, the data on short- and long-term response to tyrosine-kinase inhibitors (TKI) in different phases of CML are still scanty. It has been suggested that the early molecular respon-

se to imatinib may predict cytogenetic and clinical outcome in CML [19]. The published results of the high-dose therapy with imatinib mesylate in the chronic phase of CML are controversial [2]. The current managing approaches in CML remain vague.

Objectives: The aim of the current study was to evaluate the diagnosis assertion, the short- and long-term results and the safety of tyrosine-kinase inhibitors in patients with different phases of CML.

Materials and methods: The study enrolled 125 patients with CML, who had been followed up at the Institute of Oncology in 2005 - 2013. The type of chronic myeloproliferative disorder was identified according to the World Health Organization classification of the myeloid neoplasms, approved in 2008 [18].The diagnosis was established in chronic phase in 113 (90,4 ± 2,32%) patients, in accelerated and acute phases in (9,6 ± 2,02%) patients. Of 125 followed up patients, 86 (68.8%) were qualified and approved for GIPAP. Of patients receiving imatinib mesylate via GIPAP, 65 (87.8%) were in chronic phase and 9 (12.2%) – in accelerated and acute phases. The patient age range was 19 - 81 years, with the most frequently affected age group of 40 – 49 years (27.4 ± 4.89%). The median age was 46.1 ± 2.13 years old, that indicated the predominant involvement of the workable population. The median male/female ratio was 1.4 : 1, with the age-adjusted limits of 1.1 – 1.8 : 1. Cytogenetic analysis and real-time quantitative PCR of the bone marrow cells revealed Ph chromosome and BCR-ABL p210 transcript in all GIPAP patients. The rate range of Ph-positive cells was 20 – 100%. The rate of Ph-positive cells was more than 75% in 54 (72.7%) patients**.** Imatinib mesylate was used as a front-line therapy in 11 (14.9%) cases and in 63 (86.1%) cases of the relapse or resistance to the conventional chemotherapy. The starting dosage of imatinib varied between 400 – 800 mg daily, with respect to the CML phase [1,6,7,8,14,19]. Of 21 (28.4%) imatinib-resistant patients, 10 (13.5%) underwent therapy with dasatinib. The follow-up cytogenetic analysis of the bone marrow cells was performed within 6 to 8 months after the start of treatment with imatinib and then repeated approx. every 6 months.

Results: The extrapolation [17] showed that in the Republic of Moldova in spite of the slow increase of the incidence (2010 - 0,81‰, 2014 - 0.83‰), the prevalence of CML should grow progressively (2004 – 2.11‰, 2014 – 4.16‰). The northern (27 patients / 32.1 ± 5.10%) and central (25 patients / 29.8 ± 4.99%) regions population proved to be mainly affected by CML. 50 (59.6 ± 4.99%) patients turned to be heavily exposed to the insolation during their professional activities and daily life (correlation coefficient 0.479). The 2nd by frequency risk group of pts (27.4 ± 4.65%) comprised long-lasting smokers (over 5 years). The period diagnosis – treatment start ranged from 1 to 59 months (median – 24.7 months).

The discriminant analysis [17] of the late diagnosis factors contributed to their hierarchisation in CML în the Republica Moldova (Table 1).

The discriminant analysis, thus, revealed the higher coefficients of canonical correlation for the following late diagnosis factors: asymptomatic or oligosimptomatic onset of the disease (0.548), low level of the sanitary education of population (0.525) and the onset with indiscrete clinical and paraneoplastic symptoms (0.340).

Table 1

Hierarchisation of the late diagnosis factors in chronic myeloid leukemia

Late diagnosis factors	*Number of cases*		*Coefficient of canonical correlation*	*Hierarchisation*
	abs.	*%*		
Asymptomatic or oligosimptomatic onset of the disease	36	42.9	0.548	1
Low level of the sanitary education of population	32	38.1	0.525	2
Onset with indiscrete clinical and paraneoplastic symptoms	11	13.1	0.340	3
Misinterpretation of clinical, blood and imaging examinations data, especially at the level of primary health care	6	7.1	0.258	4
Similarity of the local clinical symptoms with those in the upper gastro-intestinal pathologies	6	7.1	0.258	4
Incomplete clinical and imaging examinations at the level of primary health care and referral hospitals	5	5.9	0.237	5
Decreased addressing of popukation to the family doctor (once per 1.5 – 2 years**)**	44	52.4	0.082	6

A complete hematologic remission was achieved in 63 (85.1%) patients within one or two months of treatment with imatinib. This was superior to the results (14 (27.5%) patients) obtained with conventional chemotherapy and interferon-α ($p<0.05$). A trend to the earlier complete hematological response was

observed in cases with chronic phase, shorter duration of CML, and lower leukocyte and thrombocyte counts ($p < 0.05$). The follow-up cytogenetic analysis of the bone marrow cells performed under the treatment with imatinib demonstrated a decrease of Ph-positive cells up to 5 – 35% in patients with a complete hematologic remission. A complete cytogenetic remission was registered in 9 (14.3%) of patients within 12–18 months of imatinib treatment. The relapse-free survival rate at 18 months proved to be much more higher ($p<0.05$) in patients treated with imatinib (82%), than in patients treated with conventional chemotherapy (20.5%).

The data demonstrated that the enrollment of CML patients in GIPAP with constant imatinib medication significantly improved ($p<0.01$) the performance status in 90.5% of them (ECOG-WHO score range 0–1, P±ES%=0.25±0.06), as compared to conventional chemotherapy. The results also showed an increase of lifespan in those CML patients with a considerable improvement of the performance status (ECOG-WHO score 1: P±ES%=46.2±8.92 months) and complete physical rehabilitation (ECOG-WHO score 0: P±ES%=51.6±4.63 months) under the treatment with imatinib (Table 2). Due to the physical rehabilitation and the improvement of quality of life, the working GIPAP patients were able to continue their professional activities.

The overall 3-year survival rate (Figure 1) in the imatinib treated patients was 66.0% and superior ($p<0.05$) to that achieved after conventional chemotherapy and interferon-α (44.5%). The median survival was superior ($p<0.05$) in the age group of 40–49 years (61.65±4.81 months) as compared with the age groups of 20–29 years (43.13±2.80 months) and over 70 years (43.14±3.92 months). The overall 3-year survival proved to be higher ($p<0.05$) in females (66%) than in males (51%).

Table 2

The lifespan of patients with chronic myeloid leukemia in regard to the ECOG-WHO score obtained under the treatment with imatinib mesylate

ECOG-WHO score	*Lifespan range, months*	*P ± ES%, months*
0	4 – 162	51.6 ± 4.63
1	9 – 156	46.2 ± 8.92
2	1 – 66	31.8 ± 11.62
3	2 – 43	26.5 ± 16.50

The overall 5-year survival in the eligible imatinib-treated patients also turned to be superior ($p < 0.05$) to that achieved after conventional chemotherapy.

The lifespan proved to be longer in CML patients under the front-line therapy with imatinib mesylate and dasatinib (Table 3).

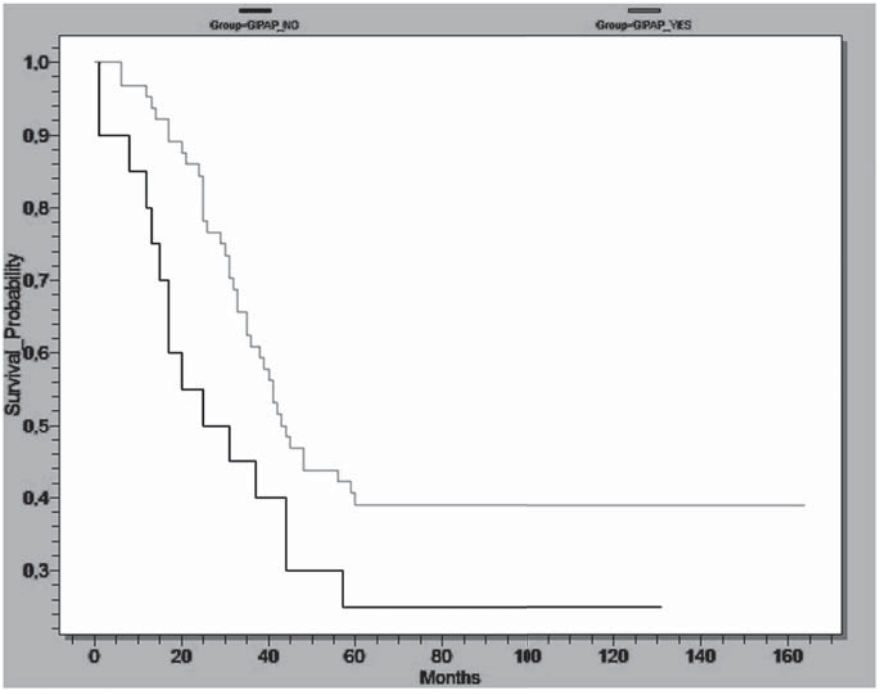

Figure 1. *Overall survival of CML patients in regard to the management options*

Table 3

The distribution by lifespan of patients with chronic myeloid leukemia in regard to the undertaken treatment modality

Ranges of patients' lifespan (months)	*Patients groups according to the treatment modality (%)*		
	conventional chemotherapy	*imatinib mesylate after conventional chemotherapy*	*imatinib mesylate and dasatinib*
≤ 12	44.1	26.5	16.7
13 - 36	23.5	70.6	83.3
37 - 60	17.7	2.9	---
≥ 61	14.7	---	---

The common side effects under the treatment with imatinib were dryness of the oral mucosa, angioedema, dyspepsia, nausea, abdominal pain, neutropenia, and thrombocytopenia, occurred in different combinations in 34.9% of cases. Marked neutropenia and thrombocytopenia developed in 11.6% of patients previously treated with busulfan and required the temporary cessation of therapy.

Of 21 (28.4%) imatinib-resistant patients, 10 (13.5%) underwent the treatment with dasatinib. Only 9 (42.9%) imatinib-resistant patients responded completely to dasatinib. Nevertheless, the complete hematologic response was achieved in all dasatinib-treated CML patients after the front-line conventional chemotherapy.

The contemporary management of CML adjusts the diagnostic and treatment options in regard with the level of medical assistance. The treatment of CML in the chronic and accelerated phases without complications may be realized in the outpatient department or in the daily stationary. CML in the accelerated phase with complications (bleeding, thrombotic, infectious) and in the acute phase should be treated in the specialized departments of hematology.

Conclusions: The combined screening for Ph chromosome, BCR-ABL p210 and p190 chimeric gene transcripts is mandatory for diagnosis and follow-up in patients fairly suspected for CML. The asymptomatic or oligosimptomatic onset of the disease, low level of the sanitary education of population and the onset with indiscrete clinical and paraneoplastic symptoms proved to be the most relevant late diagnosis factors for CML. Imatinib mesylate and dasatinib currently may be considered an effective and quite tolerable first-line targeted treatment in chronic and accelerated phases of CML, even in cases initially managed with conventional chemotherapy and interferon-α. The earliest complete hematological response may be achieved in cases with chronic phase, shorter duration of CML, and lower leukocyte and thrombocyte counts. The GIPAP mission in the Republic of Moldova results in the improvement of CML diagnosis and management, contributing to the significant increase of the life quality, relapse-free and overall survival of CML patients. The ability to obtain imatinib mesylate via GIPAP, thus, has considerably favored the outcomes for CML patients, leading to their recovery, restoration of the ability to work and social reintegration.

References

1. Baccarani M., Saglio G., Goldman J. et al., *Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet,* Blood, 2006; 108 (6): 1809 – 1820.

2. Castagnetti F., Palandri F., Amabile M. et al., *Results of high-dose imatinib mesylate in intermediate Sokal risk chronic myeloid leukemia patients in early chronic phase: a phase 2 trial of the GIMEMA CML Working Party,* Blood, 2009; 113 (15): 3428 – 3434.

3. Corcimaru I., *Leucemia granulocitară cronică.* In: Corcimaru I., "Hematologie". Chişinău: Centrul Editorial – Poligrafic *Medicina*, 2007: 178 – 189.

4. Cortes E.J., List A., Kantarjian H., *Chronic myelogenous leukemia.* In: Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media, 2004: 773 – 786.

5. Cortes J.E., Talpaz M., O'Brien S. et al., *Staging of chronic myeloid leukemia in the imatinib era: an evaluation of the World Health Organization proposal,* Cancer, 2006; 106(6): 1306 – 1315.

6. Dressman M.A., Malinowski R., McLean L.A. et al., *Correlation of major cytogenetic response with a pharmacogenetic marker in chronic myeloid leukemia patients treated with imatinib (STI 571)*, Clin. Cancer Res., 2004; 10: 2265 – 2271.

7. Durosinmi M.A., Faluyi J.O., Okany C.C. et al., *Preliminary experience with imatinib mesylate therapy of Ph+ chronic myelocytic leukaemia in Ile-Ife Nigeria*, Journal of Clinical Oncology, 2005; 23 (16S): 3216.

8. ESMO Gudelines Working Group, *Chronic myelogenous leukemia: ESMO Clinical Recommendations for diagnosis, treatment and follow-up*, Annals of Oncology, 2007; 18 (2): ii51 – ii52.

9. Kosmidis P.A., Schrijvers D., André F., Rottey S., *ESMO Handbook of Oncological Emergencies.* Taylor & Francis Group, 2005: 158 p.

10. Musteata V., *Good clinical practice in chronic myeloid leukemia: advances and prospects at the Institute of Oncology of Moldova*, Journal of BUON, 2010; 15: 188 – 189.

11. Musteaţă V., Corcimaru I., Sofroni M. et al., *GIPAP în Republica Moldova: realizări şi perspective,* Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale, 2008; 2 (16): 226 – 228.

12. Musteata V., Corcimaru I., *Targeted therapy of chronic myelogenous leukemia: experience of the Institute of Oncology of Moldova,* Archives of the Balkan Medical Union, 2008; 43 (3): 154 – 155.

13. Niederwieser D., *HSCT for chronic myeloid leukemia in adults.* In: Apperley J., Carreras E., Gluckman E. et al., Haematopoietic Stem Cell Transplantation. European School of Haematology. The EBMT Handbook. 5th Edition. Paris: Herissey, 2008: 388 – 396.

14. O'Brien S., Berman E., Devetten M.P. et al., *Chronic myelogenous leukemia. NCCN Clinical Practice Guidelines in Oncology. V 2.2009,* National Comprehensive Cancer Network, Inc., 2008: 1 – 47.

15. Ramos J.D., *Gleevec Patient Assistance Program USA. Patient Guide*. Seattle: Cancer Resources & Advocacy, 2004: 1 – 5.

16. Richard R.E., Linenberger M., *Chronic myeloid leukemia.* In: American Society of Hematology Self-Assessment Program. Blackwell Publishing, 2005: 178 – 189.

17. Spinei L., Lozan O., Badan V., *Biostatistica.* Chişinău: Tipografia Centrală, 2009: 186 p.

18. Swerdlow S.H., Campo E., Harris N.L. et al., *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th Edition.* IARC Press, Lyon, 2008.

19. Wang L., Pearson K., Ferguson J.E. et al. *The early molecular response to imatinib predicts cytogenetic and clinical outcome in chronic myeloid leukaemia*, Br. J. Haematol., 2003; 120: 990 – 999.

20. Xenocostas A., *Chronic myelogenous leukemia (CML). Hematology Practice Guideline.* London Health Sciences Centre. London Regional Cancer Program, 2007: 1 – 10.

21. Масляк З.В., *Хронічний мієлоїдний лейкоз.* In: Гайдукова С.М. "Гематологіа та трансфузіологіа". Київ: ВПЦ «Три крапки», 2001: 239 – 251.

22. Туркина А.Г., *Хронический миелолейкоз*. In: Воробьёв А.И. Руководство по гематологии. Москва: Ньюдиамед, 2003: 251 – 264.