Rezumat

Rezultatele nemijlocite şi la distanţa ale tratamentului bolnavilor de LNH au fost studiate pe un lot de 538 de pacienţi (bărbaţi – 281, femei – 257), care s-au aflat sub supravegherea în Clinica Hematologie a IMSP Institutul Oncologic din Moldova în perioada anilor 1985-2005. LNH cu grad înalt de malignitate (GÎM) au fost stabilite la 303 (56,3%) pacienţi, cu grad redus de malignitate (GRM) – la 203 (37,8%). În 32 (5,9%) de cazuri tipul morfopatologic al LNH din cauza dificultăţilor tehnice n-a fost posibil de stabilit, dar în aceste LNH au fost considerate cu GÎM. Supravieţuirea generală peste 5 ani a bolnavilor de LNH cu GÎM s-a estimat la 45,3%, de GRM – la 30,1%. S-a constatat că eficacitatea înaltă nemijlocită şi la distanţa a tratamentului pacienţilor cu LNH este în funcţie de stadiul clinic şi varianta morfopatologică.

Summary

The direct and remote results of treatment were studied in 538 cases with different histological types and clinical stages of non-Hodgkin's lymphomas (NHL). High-grade NHL were diagnosed in 303 (56, 3%) patients, low-grade NHL-in 203 (37, 8%). The histological type failed to be indentified in 32 (5, 9%) cases. The absolute majority of patients (394 or 73, 2%) had advanced stage disease. All patients underwent various treatment modalities with respect to the histological type and clinical stage. The 5-year actuarial survival of patients with low-grade NHL was 45, 3%, high-grade NHL-30, 4%. The long term survival was higher in cases with localized stage NHL. The direct and remote result of treatment in patients with NHL thus depends on the histological type and clinical stage of tumor.

UPDATED OPTIONS IN THE MANAGEMENT OF CHRONIC MYELOGENOUS LEUKEMIA IN THE REPUBLIC OF MOLDOVA

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Background: Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder resulting from the stem cell neoplastic transformation caused by translocation between the long arms of chromosomes 22 and 9 [1, 2, 3, 4, 5, 6, 16, 20, 21]. The annual incidence of CML ranges between 0.8 – 1.6 cases per 100.000 population, the disease, thus, accounts 15 – 20% of leukemias in adults [1, 2, 3, 4, 10, 16, 21]. The median age at presentation varies between 50 – 60 years. Male : female ratio may reach 1.4 : 1. CML enrolls 2% of childhood leukemia, 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 intermediates to promote leukemogenesis by changing proliferation, apoptosis, and altered interaction with the cellular matrix. The clinic-evolutional and hematologic patterns of CML comprises splenomegaly, myeloid hyperplasia of the bone marrow, hypercatabolic symptoms and progression to the acute leukemia in the majority of cases. 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]. Conventional treatment of CML includes chemotherapy, interferon-α, bone marrow transplantation [1, 2, 3, 4, 5, 6, 7, 10, 13, 14, 16, 19, 20]. In CML conventional chemotherapy doesn't reduce markedly Ph-positive cells; therefore transformation to blastic 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 in May 2001 and might be considered as a promising targeted therapy for CML. 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 its short- and long-term efficiency and safety are still scanty. The published results of the high-dose therapy with Imatinib mesylate in the chronic phase of CML are controversial [3]. The current managing approaches in CML remain vague.

Objectives: The aim of the study was to evaluate the management options, the results of implementation of GIPAP in Moldova, as well as the short-term results and the safety of Imatinib therapy in patients with different phases of CML.

Materials and methods: The study may be considered as descriptive. The following research modalities have been used: epidemiological, analytic, historical, data transfer, descriptive statistics [17]. The study enrolled 154 CML patients (58 males and 96 females) aged 14 – 74 years (median age – 40.7 years), treated and followed-up at the Hematology Division of the Institute of Oncology of Moldova between 2000 – 2009. The type of

chronic myeloproliferative disorder was identified according to the World Health Organization classification of the myeloid neoplasms, approved in 2001 [18]. The chronic phase of CML was revealed in 76 (49.4%) cases, the accelerated and acute phases – in 78 (50.6%). Of all studied CML patients, 63 (40.9%) were qualified and approved for Glivec® International Patient Assistance Program (GIPAP). Males were 30, females – 33. Of the GIPAP patients, the chronic phase of CML was revealed in 47 (74.6%) cases, the accelerated and acute phases – in 16 (25.4%). GIPAP is one of the most generous and far-reaching patient assistance programs ever developed for cancer therapy, axed on the insurance of treatment with Imatinib mesylate of different malignant neoplasms [7, 10, 11, 15]. Novartis Pharma AG is the donor organization and the manufacturer of Glivec®, supporting GIPAP by providing Glivec® to Ph-positive CML patients. Novartis Pharma AG is responsible for approving institutions recommended for participation in GIPAP as well as for shipping Glivec® to the approved patients. Since implementation, GIPAP has provided Imatinib mesylate to more than 10000 patients in 80 countries, who would not otherwise have had the access to this efficient and quite tolerable drug. The starting dosage of Imatinib varied between 400 – 800 mg daily, with respect to the CML phase [1, 6, 7, 8, 14, 19]. In 90.9% of patients Imatinib mesylate was used after the relapse or response failure to the conventional chemotherapy.

Results: Cytogenetic analysis and real-time quantitative PCR of the bone marrow cells revealed Ph chromosome and BCR-ABL p210 oncogene in all GIPAP patients. The rate range of Ph-positive cells was 20 – 100%. In 74.7% of cases the rate of Ph-positive bone marrow cells turned to be 75% and more. The period diagnosis date – Imatinib starting date ranged from 1 to 59 months (median – 24.7 months). The hematologic response was obtained in 77.9% of all CML patients. The complete hematologic response has been achieved in 81.8% of GIPAP patients within 1 – 2 months of Imatinib mesylate therapy and proved to be superior to that obtained after the usage of the conventional chemotherapy and interferon-α. The follow-up cytogenetic analysis of the bone marrow performed within 6 – 8 months of the treatment with Imatinib mesylate revealed the decrease of Ph-positive cells up to 5 – 35%. The complete cytogenetic remission has been registered in 9 (14.3%) cases within 12 – 18 months of Imatinib therapy. Patients treated with Imatinib mesylate fastly resoluted or didn't develop hematologic emergencies unlike those, who had undergone the conventional chemotherapy. Only 6 (9.5%) patients with the acute phase (blast crisis) of CML failed to respond to Imatinib mesylate.

The responding changes in the life quality of patients with CML has been evaluated in regard with the realized treatment option (table 1).

Table 1

Life quality of patients with chronic myelogenous leukemia in regard with the undertaken treatment modality

Score according to the ECOG-WHO criteria	Group of patients treated with conventional chemotherapy (%)		Group of patients treated with Imatinib mesylate (%)	
	before the treatment	after the treatment	before the treatment	after the treatment
0 (normal activities)	---	---	---	50
1	19	9,5	15	32,5
2	47,6	52,4	47,5	12,5
3	33,3	28,7	37,5	2,5
4	---	4,7	---	---
5 (self-service is impossible)	---	4,7	---	---

The employed GIPAP patients continued professional activities with the good quality of life (ECOG-WHO score 0).

The longevity of patients with CML has been studied with respect to the realized treatment option (table 2).

Table 2

Longevity of patients with chronic myelogenous leukemia in regard with the undertaken treatment modality

Longevity of patients (months)	Group of patients treated with conventional chemotherapy (%)	Group of patients treated with Imatinib mesylate after conventional chemotherapy(%)	Group of patients treated with Imatinib mesylate (%)
≤ 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 contemporary management of CML diversifies the diagnostic and treatment options in regard with the level of medical assistance. The treatment of CML in the chronic phase and accelerated phase 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 and BCR-ABL p210 / p190 oncogene is highly useful for diagnosis in patients fairly suspected for CML. The contemporary management of CML diversifies the diagnostic and treatment options in regard with the level of medical assistance. Imatinib mesylate currently remains an effective and quite tolerable targeted chemotherapeutic agent in the chronic and accelerated CML phases, even in cases initially managed with the conventional chemotherapy and interferon-α. CML history-span correlates in reverse order with the response to Imatinib. The earliest complete hematological response may be achieved in cases with chronic phase and shorter duration of CML. CML patients managed with Imatinib mesylate haven't had progression to the accelerated or blastic phases, and experienced the better response rate and quality of life, as compared with the patients treated by the conventional chemotherapy and interferon-α. GIPAP mission constitutes the improvement of lives and survival of patients with hematologic neoplasms worldwide, with the aim of delivering state-of-art technology and therapy to patients having scanty access to medical resources.

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Rezumat

Determinarea concomitentă a Ph cromozomului, genei de fuziune BCR/ABL cu proteinele himerice p210 / p190 este de importanţă practică majoră atît pentru diagnosticarea leucemiei mieloide cronice, cît şi pentru evaluarea adecvată a răspunsului la tratament. Imatinib mesilat este inhibitor al tirozinkinazei şi se aplică cu succes în toate fazele leucemiei mieloide cronice. Imatinib mesilat constituie opţiune terapeutică de prima linie în faza cronică şi de accelerare a leucemiei mieloide cronice, fiind net superioară în raport cu chimioterapie convenţională prin posibilitatea atingerii remisiunii clinico-hematologice complete şi a remisiunii citogenetice complete. Tratamentul leucemiei mieloide cronice în faza cronică şi de accelerare fără complicaţii poate fi efectuat în condiţii de ambulator sau a staţionarului de zi. Faza de accelerare cu complicaţii (hemoragice, trombotice, infecţioase) şi acută a leucemiei mieloide cronice impune tratamentul în secţiile specializate de hematologie.

Summary

The combined screening for Ph chromosome and BCR-ABL p210 / p190 oncogene is highly useful for diagnosis in patients fairly suspected for CML. The contemporary management of CML diversifies the diagnostic and treatment options in regard with the level of medical assistance. Imatinib mesylate currently remains an effective and quite tolerable targeted chemotherapeutic agent in the chronic and accelerated CML phases, even in cases initially managed with the conventional chemotherapy and interferon-α. CML history-span correlates in reverse order with the response to Imatinib. The earliest complete hematological response may be achieved in cases with chronic phase and shorter duration of CML. CML patients managed with Imatinib mesylate haven't had progression to the accelerated or blastic phases, and experienced the better response rate and quality of life, as compared with the patients treated by the conventional chemotherapy and interferon-α.

EFICACITATEA COMBINAŢIILOR CU CISPLATIN ÎN TRATAMENTUL DE LINIA II AL CANCERULUI MAMAR METASTATIC

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Actualitatea problemei puse în discuţie este marcată de faptul că tumora malignă a glandei mamare este neoplazia cea mai frecventă la sexul feminin, reprezentând circa 30% din toate cancerele feminine. Cancerul mamar condiţionează anual aproximativ 1.150.000 din totalul deceselor prin neoplazii. Incidenţa brută în Uniunea Europeană este de 105, iar mortalitatea de 40 la 100.000 de femei. Deşi prognosticul cancerului mamar primar s-a ameliorat semnificativ în ultimii ani, totuşi un număr important de paciente prezintă recidive, iar marea majoritate a acestora decedează din cauza acestei patologii.

În ciuda eforturilor depuse, cancerul mamar în stadiul metastatic (CGMM) rămâne a fi o maladie incurabilă, cu o durată medie de supravieţuire după apariţia metastazelor până la 36 de luni. Principalele modalităţi de tratament ale acestei maladii sunt reprezentate de hormonoterapie, chimioterapie, iar, în ultimul timp şi de tratamentul biologic. Tratamentul sistemic are rol, în mare măsură, paliativ, asociind tratamentul combinat şi profilaxia complicaţiilor, având ca scop prelungirea supravieţuirii fără impact negativ asupra calităţii vieţii.

Tratamentul de elecţie al tumorilor ce exprimă receptori de estrogeni şi progesteron este hormonoterapia, iar chimioterapia este prima opţiune terapeutică la pacientele endocrino-rezistente. Cele mai active citostatice s-au dovedit a fi antraciclinele, iar, mai recent, şi taxanii, urmate de citostatice alchilante, antimetaboliţi, alcaloizi de Vinca etc. Răspunsurile iniţiale au o durată medie de 8-14 luni şi progresia bolii este aproape inevitabilă. Răspunsurile complete sunt destul de rare, de obicei de scurtă durată şi doar 3-20% din pacientele la care se obţine răspuns obiectiv, îl menţin pe o perioadă mai mare de 5 ani [1]. Oricum, beneficiul rezultatelor chimioterapiei în cancerul mamar metastatic este unanim acceptat. Administrarea antraciclinelor în calitate de tratament adjuvant sau în linia I de tratament în stadiul metastatic, inevitabil provoacă şi apariţia rezistenţei la antracicline, limitând, astfel, posibilităţile terapice ale acestora. În situaţia tot mai frecventă a instalării eşecului la antracicline, apare problema tratamentului de linia a II. La moment nu există chimioterapie de linia a II universal acceptată ca standard, cu excepţia unor studii clinice de fază II, care demonstrează că Docetaxelul este eficace la pacientele cu cancer mamar rezistent la antracicline. Până în prezent importanţa chimioterapiei de linia a II este controversată, îndeosebi în ameliorarea supravieţuirii.