Prognostic Risk Factors of Prognosis of Hodgkin Lymphoma's Run: Standard and New

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Summary. Planning optimalinitial chemotherapy of patients with HL should be carried out taking into account the unfavorable risk factors. Actual questions remain for further search and study of prognostic factors that can not only predict the course of disease in general, but also to improve individual prognosis for each patient.

Key words: Hodgkin's lymphoma, risk factors, chemotherapy, prognosis, survival.

Lymphomas unite a large group of malignant tumorsof lymphoid tissue. The Hodgkin Lymphoma (HL) makes about 1% of all malignant tumorsand almost 30% of lymphomas in the world. About 8 000 new cases of the disease are annually diagnosed in the USA [1]. In Ukraine a steady tendency is kept to the increase of morbidity on malignant lymphomas, the index of increase in the regions of Ukraine for 1999-2007 made from 4,2 to 8,1 %. According to the data of the National Cancer Register, in 2010 in Ukraine more than 1000 primary patients with the Hodgkin lymphoma were diagnosed, morbidity – 2,4 and mortality– 1,1 per 100 thousand population [2].

A general 5-years survival of patients on HL makes 96,0% and lethality to year – 9,0% [3], however in Ukraine it does not exceed 71,0% and mortality to year almost in 1,5 times higher than world indexes (16,3%). In the developed countries a 5-years survival of patients of HL with advanced stages rarely exceeds 60,0%, in Ukraine it folds 45,5% patients with III and 31,4% – with IV stage [2].

Despitethe achievement of positive response on the first line of therapy in most patients, in 25-35% with HL advanced stages the relapse of the disease is found out during the first 5 years [4].

Nowadays planning of optimal chemotherapy (ChT) of primary patients with HL must be conducted taking into account a risk of unfavourable factors [5].

In the middle of the past century the first factors that allow forecasting acourse of the disease and a choice of treatment were the stage of disease and presence symptomsof intoxication.

Disease staginghas allowed to define the group of patients with a locallesion (I and II stages), for that radical radiation therapy has appeared to be the most successful [6].

Survivalanalysis of 14 000 patients with HL, conducted by research group International Database on Hodgkin's Disease (IDHD) in 1990, confirmed it.

In this research in a group of 9087 patients with local stages who got radical radiation therapy it was confirmed, that the presence symptoms of intoxication determines pooroverall survival.

Till today the system of staging, offered in Ann-Arbor in 1971 and complemented in Cotswolds in 1989, still remains the basis at forming complex of prognosticfeatures for determination of high-risk groups of patients with HL [7].

Since the 90-sof the last century it became known that mass of tumours has a not less value, than prevalence. To use the following group of prognostic risk factors was suggested by the German Hodgkin Lymphoma Study Group (GHSG) [8]:

1) an extra-nodallesion is in the limits marked with symbol E;
2) amassive lesion of mediastinum;
3) amassive lesion of spleen(≥ 5 inflammations or diffuse lesion);
4) lesion≥ 3 zones of lymph nodes;
5) on stage A ESRover 30 mm/h, on the stage B – an over 50 mm/h.

In accordance with a presence or absence of these factors patients are divided on three prognostic groups: with a favourable, intermediate and unfavourable prognosis.

Patients with I-II A-stage without risk factors refer to a group with a favourable prognosis.

Patients with I-II of A-stage with presence of risk factors, and also patients of II of B-stage with 4 and 5 risk factors and patients with III of A-stage without risk factors are unified into a group with an intermediate prognosis.

Patients with stage II B with risk factors 1-3, patients with III of A-stage with risk factors and patients with III B and IV stages are singled out in a group with an unfavourable prognosis.

Large experience of application of a radical radial therapy for patients with localized stages of the disease, accumulated till the 80-ies of the last century, has shown that, except the stage and symptoms of intoxication, there are other criteria which forecast efficiency of treatment for patients with HL [6,9]. Therefore in recent years numerous studies have been undertaken to find out additional risk factors which will allow to distinguish a group of patients withlocalized stages of the disease and to cure them only by means of radial therapy, and a group that needs the chemotherapy, are the last years undertaken.

The research, published in 1975 by M.J. Peckharnand others from Royal Marsden Hospital, showed that with localized stages of HL the risk of relapse after application of radical radial therapy depends on prevalence of the disease, which is from the amount of the initially affected zones of lymphatic collectors [10]. With lesion of 1-2 lymphatic zones the index of 7-yearsprogression free survival (PFS) in this research ran up to 70,0 %, withlesion of 3 zones – about 50,0 % and with lesion of their greater amount – only 20,0 %.In future these data were confirmed by the other research centres [9-12].

However, while realizing of multicentral analysis it has been educed, that for patients with the localized stages far more important, than amount of zones of defeat, general mass of tumour, especially at bringing in of mediastinal lymphatic nodes is. So, according to the data of Thar T.L. (1979) 10-years PFS in a group of patients with the localized stages and massive lesion of mediastinum presented 53,0 % against to 86,0 % of a group of patients with less sizes of mediastinallymphatic nodes.

These data were afterwards confirmed by numerous researches of other centres [1].

So, according to the data of the Russian Oncologic Scientific Centre (ROSC) massive lesion of mediastinum also reduces a 10-years overall survival of this group of patients from 82,0 % to 61,0 %in a group of patients without massive lesion of mediastinum. Thus, two prognosticfactors–an amount of zones with lesion and massive lesion of lymphatic nodes of mediastinum were educed [6,13, 14].

The prognostic value of the age of patients at the moment of determining the diagnosis has been proved by many researches. So, a prognostic system, recommended by EORTC (European Organization for Research and Treatment of Cancer) [15], includes as an unfavourable factor of the diseasecourse states the age of 40 years old, and NCIC/ECOG(National Cancer Institute of Canada/Eastern Cooperative Oncology Group) –over 50. Older age is associated with the poor survival of patients. However analyzing the reasons of death in the senior age-related group of patients with I-II stages of the disease byMauch P. and others the increase of death rate did not mark HL.In this group of patients frequency of death from other tumours exceeded frequency of death from progress of HL, what was explained by poorOS in the senior age-related group [16].

The Stanford Group's Research showed that the patients of the senior age-related group withlocalized stages of HL, who got the treatment taking into account the stage of disease, not corrected on the age, had had survival analogical to survival of patients in the younger age groupsgroups.

Thus, HL coursein the group of elderly patients does not differ from the course of disease in the group of young patients, however prognosis as fortolerance of treatment for oldpatients, especially intensified, which results in violation of the treatment program of and in a great deal explains differences in the indexes of survival is getting worse [9].

Unlike the group of patients with localized stages of HL, in which influence of prognostic factors on the course of disease is reflected thoroughly and on

sufficient clinical material, in the group of patients on HL from III- IV stages to this question are paid far fewer attention.

In 1995 the International Prognostic Factors Project on Advanced Hodgkin's Disease research group estimated influence of different prognostic features on the flow of disease in 5141 patients with III-IV stages of HL [17].

Influence of age, sex, histological variants of HL, IV of the stage of disease, massof tumour, symptoms of intoxication, indexes of analysis of blood(hemoglobin, leucocytes, lymphocytes and erythrocyte sedimentation rate), levels of albumin, alkaline phosphates were appraised, lactathohidraganizeand b2-micro-globulin in blood serum.

A multivariable analysis educes 7 factors that have statistically reliable influence on survival, free from failures of treatment, for patients with advanced stages of HL:

– ageover 45 years;

– male sex;

– IV stage of the disease;

– hemoglobin level < 105 g/l;

– albuminlevel inblood serum < 40 g/l;

– leucocytosis> $15x10^9$/l;

– lymphopenia< $0,6x10^9$/l;

– amount of lymphocytes in blood formula< 8 %

In a case of default of the marked prognostic factors a 5-years survival free from failures of treatment in the group of patients with advanced stages of HL, made 80,0 % and at presence of 5 factors - 45,0 %. This choice of prognostic characteristics is adopted by the International Prognostic Score (IPS). However to distinguish from a group patients with the advanced stages of HL group with a very high risk it was not succeeded by means of IPS, that is why the risk factors for stages III-IV were separately distinguished [8, 15, 17].

Nowadays mostly 3 systems of the clinical prognostic risk factors offered by large cooperative groups are used– EORTC, GHSG and NCIC/ECOG,

NCCN(National Cancer Care Network) and ESMO(European Society for Medical Oncology).

These systems differ in some way according to the complex of prognostic factors and interpretation of high-risk groups, but all of them allow attributing a patient to a certain prognostic group for the choice of the most adequate volume of treatment [18-20].

The above mentioned prognostic factors are well studied, and the use of them in everyday practice for patients with HL for the choice of the programme and volume of treatment results in the achievement of high direct and remote results: almost 90,0% total remissions (TR) for primary patients, regardless of the stage of illness; 5-yearsd survival exceeds 80-90 to every group, that allows to talk about curability of the disease at absolute majority of patients.

Until now there are still 10-20 % patients in every high-risk group, in that application of the modern chemic radial programmes is notenough effective.

Thus, today anissueon the study of tumour process at a deeper level needs to be viewed. Immunity phenotype of malignant lymphomas, a molecular-genetic profile and preventive activity today are actual and important questions in diagnostics and prognosis of course of HL in intermediate and high high-risk groups of patients.

Immunophenotype(IFT) of tumour tissue at HL is a necessary component of diagnostic process, as allows not only verifying a diagnosis but also can give important information for the estimation of disease prognosis.

At RONC named after N.N. Blohin RAMN research of clinical value of immunophenotypic parameters of tumour tissue at the various variants of HL was conducted. Immunological authentication of tumour cells at HL was conducted after histological cytoplasmic expression to the antigen of CD15, as this marker, unlike to the antigen of CD30, never expresses at non-Hodgkin lymphomas (NHL). It has been proved that for patients on cHL of CD15- the positive cells of Reed-Sternberg were determined in 67 % of cases, in 14 % of cases of cells it is not educed from expression of CD15.In addition, there was the distinguished group of

patients on HL (19%) in the tissue of that large CD15-positive tumourcells did not have the typical appearance of Reed-Sternberg cells because of that this group of patients with positive expression of this marker was distinguished with an extremely poor prognosis – frequency of complete response (CR) laid down only 64 %. At the same time, expression of CD15 or its absence on the typical cells of Reed-Sternberg in any way did not affect efficiency of therapy – frequency of CR in these cases was 87,0 % and 91,0 % accordingly (p> 0,05).Further researches in combination with determination of other biological factors of prognosis will help to define the most unfavorable groups of patients and influence on a choice of adequate programmes of HL treatment [21].

The role of expression of antigen Ki-67 in tumor cells as a risk factor of HL's unfavorable run still remain not enough studied. The Serbian group on the study of lymphomas has undertaken a study in a group of 40 patients with HL, treated according to ABVD. In this group of patients prognostic factors in IPS and expression of marker Ki-67 have been determined, that for patients with the high level of expression to the antigen of Ki- 67 and IPS > 3, there is a high risk of relapse of disease and there is a necessity for setting more intensive primary treatment [22].

Also according to the results of research of superficial cellular immunophenotyping with HL by means of CSC technology of v2.0 three additional diagnostic superficial biomarkers(membrane proteins) which in future can help to distinguish HL from similar after IFT B-cellslymphomashave been educed [23].

Lately more and more researches are being conducted in a direction of studying the inherited individual potential of organism to metabolize toxic substances and their derivatives [24]. It is known that family ofglutathione-S-transferring enzyme (GST) catalyzes conjugation of various xenobiotic (chemical agents). These enzymes have substrate specificity that includes substances with the known mutagen properties, and catalytic activity that provides the mechanism of protecting from harmful influence of these substances.

Family of enzymes of GST plays a substantial role as in metabolism of carcinogens, lipids, foods of free-radical reactions et al, so in the exchange of catacholestrogenes. GST also plays the role of a detoxifying agent, providing conjugation of genetically-toxically metabolite from glutathione, that causes their inactivation, as well as conjugation from N-acetylcystein and cystein [25].

Four basic classes of GST and few types of polymorphism of this enzyme's genes are known: GST α (alpha) GSTA, μ (mu) GSTM, θ (teta) GSTT and π (pi) GSTP [26].

GSTM μ contains zero allele in 30-60 % of people with a 0/0 genotype. Ethnic comparisons have shown that frequency of prevalence of a 0/0 genotype is less in a negroid race (35 %) than in Caucasian (49 %)

The subfamily of GSTπ includes one e glutathione-S-transferring enzyme of P1(GSTP1). A gene that encodes GSTP1 is located on the11th chromosome(11q13). Polymorphism of gene GSTP1 by one nucleotide in a 105 codon(5 axone) is the result of substituting for the nucleotide of adenine (A) on guanine (G), that results in replacement in a peptide chain of the enzyme amino acid molecule of isoleucine on a valine one (Ile→Val) [27,28]. A mutant type of allele, that encodes valine, associated with higher activity of enzyme comparatively with a wild type of allele, that is encoded by isoleucine.Except participating in the detoxication of xenobiotic, GSTP1 is also involved in adjusting of cellular proliferation and apoptosis. Allele of wild type reduces proliferate activity of cells and protects them from an apoptosis, while mutant allele does not influence on proliferation, but also protects cells from an apoptosis [28]. A wild genotype (Ile/Ile) is more often found in patients with III-IV stages of the disease and in patients with the aggressive forms of HL and bound with a high risk of relapses's development and rapid progression of the disease [29].

In modern researches the GSTP1 genotypeaccording to 105 codon is determined as an independent prognostic factor of a clinical course of the disease and the risk of relapses' rise is possible for patients with the lymphoma of Hodgkin, and also as a marker of the sensitiveness to chemotherapy [24, 30].

According to the results of Italian research of Hohaus S. and others,where they studied polymorphism of GSTT1, the authenticity is proved that the GSTT1-nullgenotype wasconnectedwith the increase of PFS in these patients, comparatively with patients, who have not got the GSTT1 genotype. On the basis of the undertaken studies the conclusion has been made, that GSTT1-null genotype can be taken into consideration as afavourableprognostic factor of the disease's flowin patients with HL [31].

The Norwegian research groups ofSarmanová J. and others in the study of biotransformation of genes in patients with HL and NHL confirms a fact, that allele of Val/Val of the GSTP1 genotype can play an extraordinarily important role in the development of the lymphoproliferativediseases [32].

It is significant to remember, that among factors which block the apoptosis of cells can also be viruses, for example virus of Epstein-Barr. Some scientists presume that the EBV virus can activate the BCL-2 protoncogene, that blocks the process of apoptosis in turn, and thus the cells of Reed-Sternberg avoid aprogrammed death [33].

It has been educed that the EBV virus is present approximately in 50 % of cells of Hodgkin and Reed-Sternberg. For patients, in which a T-cells deficit appears, and B-cellsare infected by the EBV virus, there is a risk of genetic mutations that can result in the development of the limphoproliferative diseases [34].

The role of theEBV virus as a factor of HL's courseprognosis still remains indefinite. It is an important fact, but not proved for many patients with HL [35]. According to the results of the French research a correlation of EBV-infection has been revealed in patients with HL with a microenvironment, and it is proved that a further study of an antiviral answer in patients with HL, infected by the EBV virus, can become basic for development of new treatment strategies [36].

It is considered that the virus of Epstein-Barr activates NF-kB, that starts a cascade mechanism of Fas-mediated apoptosis blocking of tumourcells. This explanation can satisfy hardly. In fact a similar mechanism that results in resistance

of tumour cells before the apoptosis is characteristic for EBV-negative cases of HL. In addition, activating of NF-kBis present in other B-cellular tumours, not associated with the infected EBV.

Farrell K. and others have confirmed a hypothesis, that cytomegalovirus of positive persons the risk of the cHL EBV-associative beginning rises, especially in elderly years. Authenticity of results on this time is compared to the independent group of control [37].

Nowadays, cytogenetic studies have been carried out, which have demonstrated a direct sequence, characteristic for clonal proliferation of cells at HL, that have characteristics of malignancy, namely, different anew location with difficult chromosomal abreaction. Unfortunately, with HL specific violations such as translocations, that give the key to a chromosomal localization of a gene or genes that take participating in etiology of HL have not been revealed.

For example, Xu C. and othersinvestigated that expression of C-Met oncogene in the cell of tumouris observed in 52 patients with HL. And although functional studies demonstrate the role of HGF/Met as a signaling pathological way in adjusting of progression of cellular cycle in L428, expression of the Met oncogene in patients with HL correlates with a favourable prognosis in two independent cohorts [38].

Vadasz Z. and others proved first, that WT-1(Wilms' of tumour gene 1) and NP-1(NEUROPILIN 1) express in endothelial cells in HL and found out that duration of angiogenesis is higher at HL, than in reactive lymph nodes, expression of factor of the vascular endothelia (VEGF) height of was below although. It could be the result of higher expression of NP-1 that strengthens the biological effects of VEGF. Thus, positive correlation was revealed between an angiogenesis and WT-1 expression. It testifies that in future WT-1 can be used as a clinical marker for HL prognosis [39, 40].

Montgomery D. and othersdetecteda high expression of chemokine TARC (CCL17) on Hodgkin and Reed-Sternberg cells in the serum of patients with HL before the beginning of the therapy. The intermediate results of research confirm

that most patients withHL of high level of TARC in plasma at the moment of clarifying the diagnosis. The high levels of TARCwhich appear during the treatment can be associated with an unsatisfactory answer on treatment and relapse on occasion; however, for some patients with a refractory disease the levels of TARC were normal [41, 42].

M'kacher R. and othersidentified activation of human neurophilicpolyomavirus (JCV), EBV virus and chromosomal instability by means of molecular research methods (FISH) identified in lymphocytes of peripheral blood in HL patients, that started to be associated with a poor prognosis, especially for patients, infected EBV by a virus(short duration of PFS, $p < 0,001$). These supervisions specify a new role of EBV and JCV in pathogenesis of HL. A status control of these viruses in further can envisage clinical direction of the disease and result in new antiviral and molecular strategies [43, 44].

Functional research of genetic associations and HLA expression in patients with HL with detected EBV virus (EBV+) and its absence (EBV-) conducted by Diepstra A. and others confirms, that a study of antigen presentation in HL pathogenesis is extremely necessary in identifying whichofantigenic peptides is attracted in the pathological process of HL arising [45-47].

That is why, a question as for relation to a further search and studies of prognostic factors, that allow not only predict the course of disease in general, but also to improve individual prognosis for every patient still remains actual.

References:

1. Diehl V., Josting A. (2004) 25 Years German Hodgkin Study Group. Munih : Medizin & Wissen, 207 p.

2. Рак в Україні, 2009–2010. Захворюваність, смертність, показники діяльності онкологічної служби / З.П. Федоренко, А.В. Гайсенко, Л.О. Гулак [та ін.] ; гол. ред. І.Б. Щепотін // Бюлетень Національного канцер-реєстру України. – К., 2011. – № 12. − С. 73–74.

3. Diehl V., Franklin J., Pfreundschuh M. et al. (2003) Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin’s disease. N. Engl. J. Med., 348: 2386–2395.

4. Lister A. (2008) Treatment of Stage IIIa Hodgkin's Disease: Long Follow-Up Perspective. J. Clin. Oncol., 26(32): 5144–5146.

5. Engert A., Diehl V., Franklin J. (2009) Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin’s lymphoma: 10 years of follow-up of the GHSG HD9 Study. J Clin Oncol., 27(27): 4548-4554.

6. Henry-Amar M., Somers R. (1990) Survival outcome after Hodgkin's disease: a report from the internationaldatabase on Hodgkin's disease. Semin. Oncol., 17(6): 758–768.

7. Демина Е.А., Тумян Г.С., Трофимова О.П. и др. (2007) Лимфома Ходжкина: лечение больных неблагоприятнойпрогностической группы. Практ. онкология, 8(2): 82–89.

8. Lister T.A., Crowther C., Sutcliffe S.B. et al. (1989) Report of a committeeconvened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswoldsmeeting. J. Clin. Oncol., 7(11): 1630–1636.

9. Демина Е.А. (2008) Лимфома Ходжкина: от Томаса Ходжкина до наших дней. Клин. онкогематология, 1(2): 114–118.

10. Имянитов Е.Н. (2007) Эпидемиология и биология лимфомы Ходжкина. Практ. онкология, 8(2): 53–56.

11. Hasenclever D. Diehl V. (1998) A prognostic score for advanced Hodgkin’s disease. International Prognostic Score Project on Advanced Hodgkin’s disease. N. Engl. J. Med., 339: 1506–1514.

12. Specht L. (1996) Prognostic factors in Hodgkin’s disease. Semin. Rad. Oncol., 6: 146–161.

13. Демина Е.А. (2002) Современное лечение лимфомы Ходжкина (лимфогранулематоза). Рус. мед. журн., 10(2): 1112–1124.

14. Stein H. (1999) Hodgkin’s disease: biology and origin of Hodgkin and Reed-Sternberg cells. Cancer Treat. Rev., 25: 161.

15. Mani H. (2009) Hodgkin lymphoma: anupdate on itsbiology with newerinsightsintoclassification. Clin. Lymphoma Myeloma, 9: 206–216.

16. Henry-Amar M., Friedman S., Hayat M. et al. (1991) Erythrocyte sedimentation rate predicts early relapse and survival in early-stage Hodgkin disease: the EORTC Lymphoma Cooperative Group. Ann. Intern. Med., 114(5): 361–365.

17. Sher D.J., Mauch P.M., VanDenAbbeele A. et al. (2009) Prognostic significance of mid- and post-ABVD PET imaging in Hodgkin's lymphoma: the importance of involved-field radiotherapy. Ann. Oncol., 20: 1848–1853.

18. Moccia M.A., Donaldson J., Chhanabhai M. et al. (2009) The International Prognostic Factor Project Score (IPS) in advancedstage Hodgkin lymphoma haslimitedutility in patients treated in the modernera. Blood, 114: 1554.

19. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hodgkin Disease/ Lymphoma.V.2.2008. [електронний ресурс]. – режим доступу : http://archives.who.int/professionals/physician_gls/PDF/hodgkins.pdf

20. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hodgkin Disease/Lymphoma.V.2.2012. [електронний ресурс]. – режим доступу : http://archives.who.int/professionals/physician_gls/PDF/hodgkins.pdf

21. Josting A., Rueffer U., Franklin J. et al. (2000) Prognostic factors and treatment outcome in primary progressive Hodgkin lymphoma: a report from the German Hodgkin Lymphoma Study Group. Blood, 96(4): 1280–1286.

22. Тумян Г.Н., Тупицын Н.Н., Пробатова Н.А. и др. (2008) Иммунологические критерии прогноза при лимфоме Ходжкина. Онкогематология, 1(1): 44–49.

23. Ljubomir J. et al. (2009) Poor outcome in patients with diffuselarge B-cell lymphoma isassociated with high percentage of bcl-2 and Ki 67-positive tumor cells. Vojnosanit. Pregl., 66(9): 738–743.

24. Hofmann A. et al. (2010) Mass-spectrometric cell surfaceprotein phenotyping of Hodgkin Lymphoma. Eur. J. Haematol., 95, suppl. 4: 3.

25. Hayes J.D., Pulford D.J. (1995) The glutathione S-transferase supergenefamily: regulation of GST and the contribution of the isoenzymes to cancerchemoprotection and drugresistance. Crit. Rev. Biochem. Mol. Biol., 30(6): 445–600.

26. Conney A.H., Zhu B.T. (1998) Functionalrole of estrogenmetabolism in targetcells: review and perspectives. Carcinogenesis, 19: 1–27.

27. Hayes J.D., Flanagan J.U., Jowsey I.R. (2005) Glutathione transferases. Ann. Rev. Pharmacol. Toxicol., 45: 51–88.

28. Holley S.L., Frye A.A., Haycock J.W. et al. (2007) Differential effects of glutathione S-transferase pi(GSTP1) haplotypes on cell proliferation and apoptosis. Carcinogenesis, 28: 2268–2273.

29. Gustavo J., Iramaia A., Sforni C.S. et al. (2010) Polymorphisms of glutathione-S-transferase Mu 1, glutathione S-transferase theta 1 and glutathione S-transferase Pi 1 genes in Hodgkin's lymphoma susceptibility and progression. Leukemia & Lymphoma, 50(6): 1005–1009.

30. Колісниченко Л.С., Кулінський В.І. (1999) Глутатіонтрансферази. Успіхи сучасної біології, 107(3): 179–191.

31. Hohaus S., DiRuscio A., DiFebo A. et al. (2005) Glutathione S-transferase P1 genotype and prognosis in Hodgkin’s lymphoma. Clin. Cancer Res., 11: 2175–2179.

32. Hohaus S., Massini G., D’Alo F. et al. (2003) Association between glutathione S-transferase genotypes and Hodgkin’s lymphoma risk and prognosis. Clin. Cancer Res., 9: 3435–3440.

33. Sarmanovaґ J., Benesovaґ K., Gut I. et al. (2001) Geneticpolymorphisms of biotransformationenzymes in patients with Hodgkin’s and non-Hodgkin’s lymphomas. Hum. Mol. Genet., 10(12): 1265–1273.

34. Kamper P., Bendix K., Hamilton-Dutoit S. et al. (2011) Tumor-infiltratingmacrophagescorrelate with adverse prognosis and Epstein-Barr virusstatus in classical Hodgkin's lymphoma. Haematologica, 96(2): 269–276.

35. Yucesoy B., Johnson V.J., Kashon M.L. et al. (2005) Lack of associationbetweenantioxidant gene polymorphisms and progressive massivefibrosis in coalminers. Thorax, 60: 429–492.

36. Asano K. et al. (2009) A genome-wide association study identifiesthreenew susceptibility loci for ulcerativecolitis in the Japanesepopulation. Nat. Genet., 41(12): 1325–1329.

37. Chetaille B., Bertucci F., Finetti P. et al. (2009) Molecularprofiling of classical Hodgkin lymphoma tissuesuncoversvariations in the tumor microenvironment and correlations with EBV infection and outcome. Blood, 113: 2765–3775.

38. Farrell K. et al. (2010) Seropositivity for humancytomegalovirusisassociated with anincreasedrisk of both EBV-negative and EBV-positiveclassical Hodgkin Lymphoma. Eur. J. Haematol., 95(suppl. 4): 2.

39. Xu C. et al. (2010) Expression of the C-Met oncogenecorrelates with favorable progression freesurvival in classical Hodgkin Lymphoma. Eur. J. Haematol., 95(suppl. 4): 1.

40. Vadasz Z. et al. (2010) Is WT-1 a new Pro-ahgiogenicmarker in Hodgkin Lymphoma? Eur. J. Haematol., 95(suppl. 4): 6.

41. Gutierrez A., Mestre F., R. Ramos et al. (2009) Vascularendothelialgrowthfactor (VEGF) expressionbyneoplastic hodgkin-reed-sternberg cellsisanindependentadverse prognostic factor for relapse in Hodgkin lymphoma. Blood, 114: 1561.

42. Montgomery D. et al. (2010) Pilot study to assesss the clinical of Tarcas a biomarker in Hodgkin Lymphoma. Eur. J. Haematol., 95(suppl. 4): 8.

43. Hsi E. (2008) Biologicfeatures of Hodgkin lymphoma and the development of biologic prognostic factors in Hodgkin lymphoma: tumor and microenvironment. Leuk. Lymphoma, 49(9): 1668–1680.

44. M'kacher R. et al. (2010) JC Humanpolyomavirusisassociated to chromosomalinstability in peripheralbloodlymphocytes of Hodgkin Lymphoma patients and orclinical outcome. Eur. J. Haematol., 95(suppl. 4): 12.

45. Sranchez-Espiridiron B., Montalban C., Lopez A. et al. (2010) A molecularrisk score based on 4 functionalpathways for advancedclassical Hodgkin lymphoma. Blood, 116(8): e12–e17.

46. Diepstra A. et al. (2010) HLA expression and geneticassociations in EBV positive and EBV negativeclassical Hodgkin Lymphoma. Eur. J. Haematol., 95(suppl. 4): 12.

47. Steidl C., Lee T., Shah S.P. et al. (2010) Tumor-associatedmacrophages and survival in classic Hodgkin's lymphoma. N. Engl. J. Med., 362: 875–885.