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R.K. KARAKULOV[1], *S.T. GABBASOVA*[1], *M.K. KARAZHANOVA*[1], *B.A. NASIPOV*[1], *M.V. MIRZAEVA*[1]

[1]Kazakh Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan

Immune polychemotherapy regimen choice in B-cell non-Hodgkin lymphoma of high and low malignancy based on the identification of the mutational c-myc gene and BCL2

Relevance: *Studying gene expression profiles to identify molecular subgroups of B-cell non-Hodgkin lymphomas (B-NHL) is a topical issue of cancer hematology. It allows a personalized approach to the treatment of B-NHL using high-dose polychemotherapy (PCT) with a monoclonal antibody. Such an approach improves the immediate treatment efficacy and event-free survival of patients. In this sense, it is important to determine the expression of c-myc and BCL2 genes in tumors as their presence controls chemotherapy resistance. In this study, the gene expression profiling served to identify molecular subgroups in patients with B-NHL to administer personalized treatment.*

The study *aimed to analyse the frequency and role of c-myc and BCL2 proteins expression in patients with B-NHL and compare the obtained molecular genetic and immunohistochemical test results to the clinical data.*

Results: *The use of high-dose PCT in the R+HyperCVAD regimen (6 courses) followed by hemopoietic stem cell autotransplantation in 7 (15,9%) out of 44 patients with co-expression of the c-myc mutational gene and BCL2 and with high Ki 67 values has improved the immediate efficacy of treatment; the complete response amounted to 80%; the event-free survival was 22 months. The patients with no mutational gene but with high BCL2 and Ki 67 values received 6 courses of PCT in the R-CHOEP regimen, what resulted in the complete response in 70.0±6.6% of cases and partial response in 30.0±4.0% of cases. No disease progression was registered.*

Conclusions: *The study of molecular genetic features of 44 patients with B-NHL has revealed the expression c-myc mutational gene and BCL2 in 7 out of 44 patients. These cases were characterized by an aggressive course and a "poor" response to therapy what predetermined the use of high-dose PCT with autologous stem cell transplantation.*

Keywords: *B-cell lymphoma, c-myc mutational gene, BCL2 high-dose polychemotherapy with hemopoietic stem cell autotransplantation.*

Introduction.

Non-Hodgkin B-cell lymphomas are stratified based on clinical and laboratory parameters according to the International Prognostic Index (IPI) criteria into low, intermediary, and high-risk groups. This stratification correlates with overall survival and event-free survival indexes [1]. Among oncogenic events, c-myc gene recombination is revealed in 5-14% cases of diffuse large B-cell lymphoma (DLBCL) and is associated with an aggressive course and poor prognosis [2].

In 20-30% of DLBCL cases, the chromosomal translocation t(14;18)(q32;q21) is combined with the bcl-2 oncogene hyperactivation and an increased accumulation of its product, the bcl-2 protein, which is essential in the suppression of apoptosis. Less common is the chromosomal translocation t(8;14)(q24;q32) associated with the overexpression of the c-myc oncogene which encodes the protein that regulates proliferation, differentiation, and apoptosis. This anomaly is more typical for Burkitt's lymphoma but is also detected in 5-15% of DLBCL.

BCL2 recombination is found in 17% of B-NHL, BCL 6 recombination – in 20-24% of B-NHL [3]. GCB-DLBCL demonstrates increased expression of bcl-2 and, often, c-myc. ABC-DLBCL is accompanied by a translocation involving the bcl-6 gene and p53 inactivation, in some cases. The patients with GCB-type lymphoma have a better average response to standard chemotherapy and a better prognosis [4].

The identification and development of various biological markers can give a better view on molecular-biological features of NHL and create opportunities for a personalized treatment considering characteristics of a particular patient's tumor. Therefore, the main purpose was to study the efficacy of B-cell lymphoma molecular genetic profiling to improve and introduce innovative approaches in diagnostics and prognosis [5, 6].

The study aimed to analyze the frequency and role of c-myc and BCL2 proteins expression in patients with B-NHL and compare the obtained molecular genetic and immunohistochemical test results to the clinical data.

Materials and Methods.

Forty-four patients with histologically and IHC verified B-NHL were FIST-tested and received immune polychemotherapy followed by hemopoietic stem cell autotransplantation.

Inclusion criteria: primary patients above 18 years with a histologically and IHC (BCL2) verified B-cell lymphoma, proliferative activity (Ki 67) and tumor staging. ECOG performance status – 0 or 1. Other inclusion criteria: ANC ≥1,000/μl, PLT CNT ≥50,000 / μl, serum creatinine and urea levels ≤1.5x ULN, ALT, and AST ≤2.5x ULN.

1. All patients underwent breast CT, abdomen MRI and ultrasonography, and PET-CT to register the tumor response.

2. All patients with B-cell lymphomas underwent molecular genetic testing to reveal the c-myc (8;14) and BCL2 genetic mutation for the choice of personalized treatment.

3. The patients were divided into high and low-risk groups. The chemotherapy regimen was chosen, taking into account the results of cytogenetic studies.

4. The patients with highly malignant B-NHL with co-expression of c-myc gene and BCL2 received 6 courses of high-dose PCT in R+HyperCVAD regimen including immune therapy (Rituximab 375 mg/m2 on Day 1, CF 300 mg/m2, twice a day on Days 2-4, Mesna 600 mg/m2 on Days 2-4, an intravenous 72 hourly infusion of Doxorubicin 16.7 mgm2 on Days 5-7, Vincristine 1.4 mg/m2 on Days 5 and 12, and Dexamethasone 40 mg I.V. on Days 2-5 and 12-15) followed by haemopoietic stem cell autotransplantation.

5. The patients with low malignant B-NHL with no c-myc mutation but with high BCL2 and Ki 67 values received PCT in the routine R+CHOP regimen and R+CHOEP regimen with a monoclonal antibody (Rituximab 375 mg m/2 on Day 0, Cyclophosphamide 675 mg/m2 on Day 1, Doxorubicin 40 mg/m2 on Day 1, Vincristine 1, 4 mg I.V. on Day 1, prednisone 40 mg/m2 I.V. on Days 1-5, Etoposide 100 mg m/2 on Days 1-3 I.V.) the patients with low BCL2 and Ki 67 values received PCT in the R+CHOP regimen.

6. The efficacy of treatment was assessed by the improvement of clinical laboratory and instrumental tests (CBC, LDH, ALP, X-ray, ultrasound, CT, MRI, and PET-CT).

FISH test. Fluorescence *in situ* hybridization (FISH) is based on the use of fluorescent DNA probes. These probes are artificially synthesized DNA fragments (oligonucleotides) with the sequence that is complementary to the DNA sequence of the aberrant chromosomes under study. We utilized the probe Vysis myc Break-Apart FISH Probe Kit by Abbott, namely, Vysis DNA probes RUNX1/RUNX1T1DF: 2G 2O. Vysis DNA probes IGH /MYC/ CEP 8 2G2O2A.

After denaturation, the DNA molecule acquires the form of a single-stranded yarn. The DNA probe hybridizes (binds) to its complementary nucleotide sequence and can be detected using a fluorescence microscope with a double filter (Green/Orange). At least 50 nuclei in four different tumor zones are required for evaluation purposes. The presence of a "Fusion" signal in chromosome 8 in the green-orange spectrum is considered a positive result which is expressed as a percentage. The detection of c-myc rearrangement during B-cell lymphoma diagnostics worsens the prognosis and requires an aggressive approach to the first line of treatment. In the absence of aberrant chromosomes, unbound DNA probes are "washed off" during the reaction. On a fluorescent microscope, this is defined as the absence of a fluorescent signal (a negative FISH test result). This method allows evaluating not only the presence of a fluorescent signal but also its intensity and localization. Thus, the FISH test provides also a quantitative result. The samples were analyzed under a fluorescent microscope using appropriate cubic filters. At least 50 cells were counted in each sample.

The primary evaluation points included: the primary tumor size and localization as per the X-Ray examination, abdominal and chest CT, MRI, and ultrasonography of peripheral and retroperitoneal lymph nodes, CBC, blood biochemistry (LDH, ALP), tumor substrate IHC, myelogram, cytogenetic data, immunologic examination, and ECOG performance status.

The *secondary evaluation endpoints* included: tumor regression rate (complete, partial regression) based on the tumor size reduction data, the relief of intoxication symptoms, the improvement of X-ray, CT, MRI, PET-CT, ultrasound, CBC and biochemical test results (LDH, ALP), the myelogram data after 4-6 courses of PCT, as well as the ECOG performance status and event-free survival of the patients.

Results and Discussion:

1. The efficacy of B-NHL treatment based on the study of the mutational gene c-myc

We have analyzed the treatment outcome of 44 patients with B-cell lymphomas stages II-IV A & B treated at the Center for Hematological Malignancies and Bone Marrow Transplantation of Kazakh Institute of Oncology and Radiology (KazIOR, Almaty, Kazakhstan). Of these, three patients had Burkitt's lymphoma stage IVB, and 41 had DLBCL, including four patients with primary brain damage.

The patients (18 men and 26 women) were aged 27 to 58 years, with an average age of 42 years. B-cell lymphoma was confirmed in all cases; all patients had CD20 antigen expression confirmed by IHC test. Five patients had high Ki 67 values ranging 70 to 98% (average 83.0 ± 4.6%), i.e., their tumors tended to be aggressive.

The FISH test revealed a co-expression of the mutated c-myc gene and BCL2 in 7 out of 44 patients with B-NHL (Figure 1). Therefore, their tumors were classified as highly malignant and required high-dose PCT with a monoclonal antibody Rituximab followed by stem cell autotransplantation. The threshold levels of c-myc (40.0%) and BCL2 (70.0%) in those patients indicated adverse treatment outcomes.

35 out of 44 patients had no mutational gene c-myc; therefore, their tumors were classified as low malignant.

High Ki 67 values in tumors with co-expression of the mutational gene varied from 80 to 100%, medium values – 60 to 76%, and low values – 35 to 57%; BCL2 values varied from 50 to 66%, 37 to 46%, and 25 to 32%, respectively (Table 1).

Table 1 – Co-expression of Ki 67 and BCL2 genes in patients with B-cell NHL

Threshold levels / Level of expression	Ki 67, in %	BCL2, in %
High	80.0 – 100.0	50.0 - 60.0
Medium	60.0 – 76.0	37.0 - 46.0
Low	35.0 – 57.0	25.0 – 32.0

S. Hu et al. reported 3-year total survival of 43 and 86% and the event-free survival of 39 and 75% in the patients [7] with the co-expression of the mentioned genes after treatment in the R-CHOP regimen.

Seven out of 44 patients, including three patients with primary brain damage and three patients with Burkitt's lymphoma, have received 6 courses of high-dose PCT in the R+HyperCVAD regimen. Afterward, five patients underwent stem cell autotransplantation of 4-4.8 million stem cells.

By the end of the 6th PCT course, three patients with Burkitt's lymphoma showed partial regression of the tumor process (over 80%), significant regression of the conglomerate of peripheral lymph nodes (by 75-80%) and the relief of intoxication and pain symptoms. One patient with Burkitt's lymphoma stage IVB had manifestations of all intrathoracic lymph nodes on CT followed by a partial regression of the tumor after 6 PCT courses in the R+HyperCVAD regimen and hemopoietic stem cell autotransplantation.

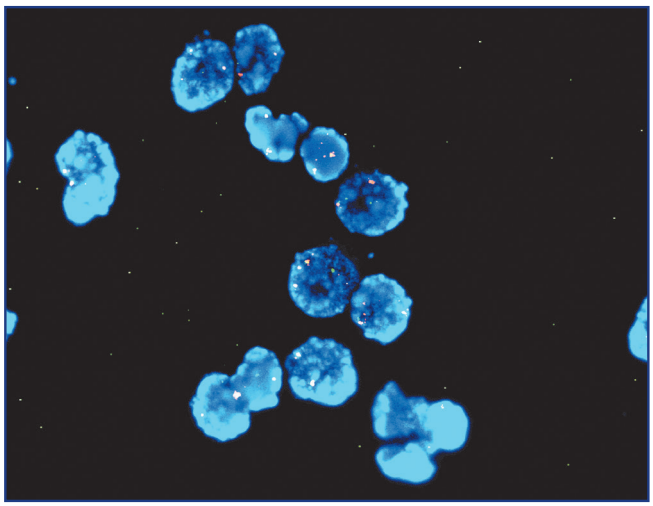

Figure 1 – c-myc gene amplification on the FIST image of histological sections of the patient M, 56 years. Probe Vysis MYC Dual Color

All patients with Burkitt's lymphoma had marrow bone damage. Three patients with primary B-NHL of the brain had the 70% regression of the primary focus compared with its original size, and the 80% regression of the peripheral lymph nodes. The marrow bone was intact.

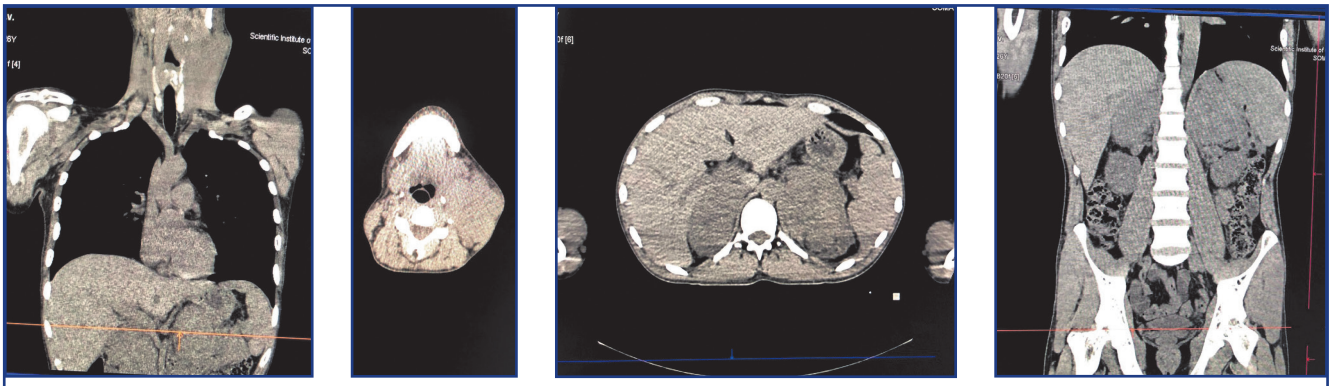

Figure 2 – Multi-layer spiral CT before treatment. Patient M., 56 y.o.

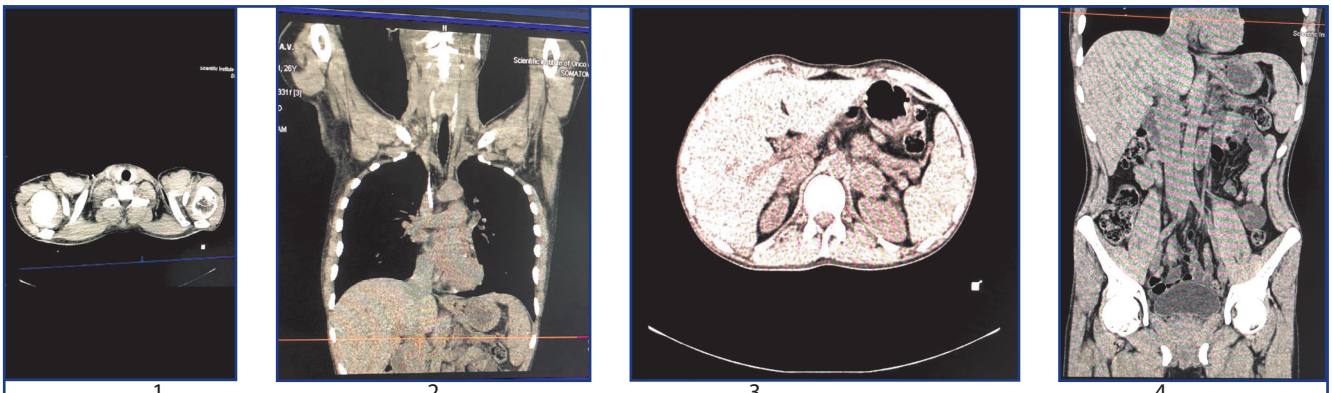

Figure 3 – Multi-layer spiral CT after treatment. Patient M., 56 y.o.

The lab tests have shown the relief of intoxication and anemia symptoms, and ESR reduction up to 18mm/h in all cases. Before treatment, the protein-forming and detoxification functions of the liver were significantly depressed in patients with DLBCL in both arms. The patients also suffered from hypoproteinemia; after treatment, the protein content has equally increased in both arms by an average of 10 g/L. AST, ALT, total bilirubin and creatinine levels were quite high before treatment and decreased after treatment by an average of 3 times compared with the control arm, while LDH and alkaline phosphatase have decreased by 2-3 times vs. the baseline (p = 0.05) (Table 2). Blood chemistry tests have shown positive dynamics after treatment. Thus, total bilirubin was 13.1 μmol/L; total protein – 65 g/L; creatinine – 80 mmol/L; LDH –131mmol/L; ALP – 85mmol/L; ALT and AST levels were within the permissible limits. Repeated myelogram registered no bone marrow damage after three courses of PCT.

The side effects of PCT, which included deep cytopenia, febrile neutropenia, and the emetic syndrome, were stopped after a symptomatic therapy. The post-treatment activity of the patients on the ECOG-WHO scale was 1 point. In all cases, the event-free survival exceeded 18 months.

Table 1 – Blood chemistry in patients after PCT (R+HyperCVAD)

Indicators	Before treatment	After 3 courses of PCT
Total protein, g/L	56.5+3.4	65.0+4.6
ALT, U/L	7.8+0.8	1.76+0.08
AST, U/L	6.6+0.05	1.9+0.03
LDH, U/L	356+4.3	131+12.9
Alkaline phosphatase, U/L	198.0+2.0	85.0+4.2
Creatinine, mmol/L	130+2.8	80+0.8

Five patients with identified C-MYC mutational gene underwent stem cell autotransplantation of 4-4.8 million stem cells and received 6 PCT courses in the R+HyperCVAD regimen. The partial remission by 80% of all groups of peripheral lymph nodes and more than 60% of the left mandibular formation was achieved. The patient will continue receiving PCT in the mentioned regimen. The quality of life after treatment was 1 point by ECOG -WHO scale.

2. The efficacy of B-cell lymphoma stages II-IV A&B treatment without the identified c-myc gene

This arm included 35 patients with B-NHL stages II-IV A&B without the identified c-myc gene. Of them, 25 patients had low malignant NHL (indolent form) (Ki 67 – 35-57%, BCL2 – 25-32%), and the other 14 patients had highly malignant NHL with Ki 67 ranging from 80 to 100%. All those patients had II-IVA and B stages of the process. The myelogram showed bone marrow damage in 40% of patients.

The patients with low aggressive tumor received 6 PCT courses in the R+CHOP 21 regimen for the process consolidation. At that, 20 patients (80.0±10.0%) had a complete remission of the tumor; the remaining 5 patients (20.0±5.3%) had partial remission. No tumor progression was observed during treatment. It can be assumed that immune polychemotherapy is more efficient in B-NHL with low proliferative index vs. B-NHL with high proliferative index.

The remaining 14 patients with high levels of Ki 67 (87.0%) and BCL2 (53.0%) without the identified mutational gene have received 6 PCT courses in the R-CHOEP 21 regimen. At that, 70.0±6.6% of patients had a complete remission of the tumor vs. 30.0±20.0% of cases of partial remission. No tumor progression was registered.

Thus, the preliminary outcome of 7 patients with DLBCL and the identified c-myc gene who received treatment in the R+HyperCVAD regimen, including immunotherapy shows the efficacy of high-dose chemotherapy. The complete tumor response to treatment was achieved in 80% of cases, and the event-free survival has exceeded 22 months.

Gene expression profiling reveals several subtypes of B-cell lymphoma: those that originate from the germinal center B-cells and those that originate from activated B-cells. The c-myc, bcl 6, and BCL2 genes are the key regulators of B-lymphocyte development at the level of germinal (follicular) differentiation. Determination of abnormalities of these genes and the quantitative parameters of expression of proteins they code will allow identifying risk groups among patients with DLBCL with high probability. About 5-14% of cases of DLBCL are associated with c-myc gene recombination [8-9]. We have shown that such c-myc gene recombination is associated with an aggressive course and worse survival of patients with DLBCL. According to the literature data, in most cases, DLBCL with c-myc recombination manifests with extranodal lesions, a late stage of the disease (stage III-IV by Ann-Arbor classification). Tumor cells are characterized by a high proliferative index Ki-67 (> 80%). Such patients have lower overall survival, a worse response to R-CHOP therapy compared with cases without c-myc recombination; the relapses involving CNS are more frequent [8, 10].

As in our study, S. Hu et al. [7] have compared the IHC, FISH, and gene profiling results with clinical data to show that DLBCL cases with MYC/NCL2 co-expression (threshold level of 40.0% for c-myc and 70.0% for BCL2) have the most adverse treatment outcomes. In the study of the results of 193 patients with DLBCL made by T.M. Green et al. [11], MYC/ML2 co-expression correlated with an adverse prognosis when using R-CHOP regimen (3-year overall survival 43 vs. 86%, event-free survival 39 vs. 75%). In the group with MYC/ML2 co-expression, FIST-tests have shown genetic abnormalities of the relevant

genes in 54% of patients. The prognostics factor of MYC/ML2 co-expression was statistically significant when taking into account other factors (for example, IPI, belonging to the GCB / non-GCB subtype, the presence of C-MYC / BCL2 rearrangements) [12, 13].

In our study of molecular genetic features of B-cell lymphomas, we have revealed biological varieties and identified several genetic subtypes of this disease which differ in their course and prognosis. B-cell lymphoma subtypes develop from genetic disorders in the process of B-cell lymphocyte differentiation/maturation and are characterized by blocking apoptosis, impaired bcl-2 regulation, loss of bcl-6 function, p53 deletion, and increased cell proliferation, as well an interrupted c-myc adjustment. GCB-DLBCL is characterized by impaired adjustment of increased expression of bcl-2 and, often, c-myc. ABC-DLBCL is accompanied by a translocation involving the bcl-6 gene and, in some cases, by p53 inactivation. Patients with GCB-type lymphoma have a better average response to standard chemotherapy and a better prognosis. We consider that in aggressive B-cell lymphomas, the classical NF-kB activation and the impaired c-myc regulation lead to refractoriness towards standard chemotherapy. The solution to that could be a high-dose polychemotherapy with a monoclonal antibody (R+HyperCVAD).

The empirical approach to the choice of anticancer therapy is getting out of date. The new knowledge about the tumor cell functioning along with the identification of drug targets and insufficient effectiveness of cytostatics motivate to look for options for individual-specific therapy based on molecular markers.

This paper mainly focuses on the analysis of chromosomal changes in tumor elements. Without this data, modern diagnostics of blood diseases of tumor nature, their prognosis and choice of rational therapy are either impossible or prone to significant errors.

In their studies of DLBCL molecular genetic properties, many authors have revealed biological varieties and identify several genetic subtypes of this disease that differ in their course and prognosis. Therefore, our study focused on the efficacy of molecular genetic profiling of lymphoid system tumors to improve and introduce innovative approaches in diagnosis and treatment prognosis [1, 12, 13].

Our study of molecular genetic features of B-cell lymphoma has revealed the co-expression of c-myc and BCL2 genes in 7 out of 44 patients with B-NHL. The use of high-dose immune chemotherapy has identified several genetic subtypes of this disease which differ in their course and the response to treatment. The use of high-dose PCT followed by hemopoietic stem cell autotransplantation in patients with co-expression of the c-myc gene and BCL2 has shown high efficacy of the therapy and justified our prognosis of treatment effectiveness.

Conclusions:

1. We have identified a correlation between the proliferative activity of the tumor (Ki 67) and the c-myc gene detectability.

2. High-dose PCT in the R+HyperCVAD regimen (6 courses) in patients with identified mutational gene has improved the immediate efficacy of therapy. The complete response amounted to 80.0%; the event-free survival has exceeded 22 months.

3. In patients with high BCL2 and Ki 67 levels without an identified mutational gene, 6 courses of PCT in the R-CHOEP 21 regimen resulted in complete remission in 70.0±6.6%, and partial remission – in 30.0±20.0% of patients. No disease progression was registered.

4. The event-free survival of patients with c-myc and BCL2 co-expression was 22 months.

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ТҰЖЫРЫМ

Р.Қ. Қарақұлов[1], С.Т. Ғаббасова[1], М.К. Каражанова[1], Б.А.Насипов[1], М.В.Мирзаева[1]

[1]«Қазақ онкология және радиология ғылыми-зерттеу институты» АҚ, «Гематология және сүйек кемігін ауыстыру орталығы»,
Алматы қ., Қазақстан Республикасы

Мутацияланған C-NYC, BCL 2 гендерін идентификациялау арқылы В-жасушалы Ходжкиндік емес лимфомасының жоғарғы және төменгі дәрежелі белсенділігіне байланысты иммундық химиялық емді таңдау

Өзектілігі. *В-жасушалық ходжкиндік емес лимфаманың (ХЕЛ) молекулалық топшаларын сәйкестендіру үшін гендер экспрессиясының профилін зерттеу онкогематологияның өзекті мәселесі болып табылатыны анықталды, өйткені моноклоналды антиденені қамтитын жоғары дозалы ПХТ режимін қолдана отырып, ходжкиндік емес лимфамамен ауыратын ХЕЛ пациенттерді емдеуде жүргізіліп жатқан дербестендірілген тәсіл емнің тікелей тиімділігін және пациенттердің өмір шеңдігін арттыруға мүмкіндік береді. Бұл аспектіде ісіктердің c-myc және BCL 2 генінің экспрессиясын анықтау маңызды рөл атқарады. Осы зерттеуде гендер экспрессиясының профилін зерттеу В-жасушалық ходжкиндік емес лимфамамен ауыратын ХЕЛ науқастарда молекулалық топшаларды сәйкестендіру және кейіннен оларға дербестендірілген ем тағайындау үшін жүргізілді.*

Зерттеу мақсаты: *В-жасушалы ХЕЛ бар науқастарда c-myc және BCL 2 ақуыз экспрессиясының жиілігі мен рөлін талдау және молекулярлық-генетикалық және иммуногистохимиялық зерттеулердің нәтижелерімен клиникалық мәліметтермен салыстыру.*

Нәтижелері: *В - жасушалы ходжкиндік емес лимфамамен ауыратын (ХЕЛ) 44 науқаста 37 C-NYC, BCL 2 гендерінің ко - экспрессиясы анықталғанда 6 мәрте жоғарғы мәлшердегі R+HyperCVAD иммундық химиялық емі жүргізілді және сүйек кемігінің аутотрансплантациясы жасалынды. Бұл жағдайда ісіктің толық ремиссиясы /ТР/ 80,0%, ал аурудың қайталанбай өмір сүру мерізімі 22 айды құрады. BCL 2 және Ki67 жоғары мәндегі мутациялық гені анықталған емделушілерде R-CHOEP 21 схемасы бойынша ПХТ 6 курсын өткізу 70,0±6,6%, ішінара – 30,0±4,0% науқастарда толық ремиссияға (ПР) қол жеткізуге мүмкіндік берді; аурудың өршуі тіркелмеді.*

Қорытынды: *В-жасушалы Ходжикиндік емес лимфомамен ауыратын 44 науқастың молекулалық-генетикалық ерекшеліктерін зерттеу 44 науқастың 7-нен c-myc және BCL 2 мутациялық генінің ко-экспрессиясын анықтады. Осы аталған жағдайлар аурудың агрессивті ағымымен ерекшеленіп, емге «кері» әсер етті, бұл аутологиялық дің жасушаларын ауыстырумен жоғары дозалы ПХТ-ны қолдану қажеттілігін алдын ала анықтады.*

Түйінді сөздер: *В-жасушалы лимфома, c-myc, BCL 2 мутациялық гені, ГСК аутотрансплантациясы бар жоғары дозалы полихимиотерапия.*

АННОТАЦИЯ

Р.К. Каракулов[1], С.Т. Габбасова[1],М.К. Каражанова[1], Б.А Насипов[1], М.В. Мирзаева[1]

[1]АО «Казахский НИИ онкологии и радиологии», Центр гематологии
и трансплантации костного мозга»
г.Алматы, Республика Казахстан

Выбор режима иммунополиихимиотерапии при В-клеточной неходжкинской лимфоме высокой и низкой степени злокачественоти на основе идентификации мутационного гена c-myc и BCL 2

Актуальность: *Установлено, что изучение профиля экспрессии генов для идентификации молекулярных подгрупп В-клеточных неходжкинских лимфом (НХЛ) является актуальной проблемой онкогематологии, ибо персонифицированный подход в лечении пациентов с НХЛ с применением режима высокодозной ПХТ, включающий моноклональное антитело позволяет увеличить непосредственную эффективность проводимой терапии и бессобытийной выживаемости пациентов. В этом аспекте важную роль играет определение экспрессии гена c-myc и BCL 2 в опухолях, присутствие которых обусловливает резистентность к химиотерапии. В данном исследовании изучение профиля экспрессии генов проводилось для идентификации молекулярных подгрупп у больных с В-клеточными НХЛ и последующего назначения им персонифицированного лечения.*

Цель исследования: *анализ частоты и роли экспрессии белков c-myc и BCL 2 у больных с В-клеточными НХЛ и сопоставление с результатами молекулярно-генетического и иммуногистохимического исследований с клиническими данными.*

Результаты: *Применение высокодозной ПХТ у 7 больных из 44 по схеме R+HyperCVAD (6 курсов) и аутотрансплантации ГСК при ко-экспресии мутационного гена c-myc, BCL 2 и с высокими значениями Ki 67 позволило улучшить непосредственную эффективность терапии, при этом частота полной ремиссии составляет 80%, бессобытийная выживаемость – 22 мес. У пациентов без выявленного мутационного гена с высоким значениями BCL 2 и Ki 67 проведение 6 курсов ПХТ по схеме R-CHOEP 21 позволило достичь полной ремиссии (ПР) у 70,0±6,6%, частичной – у 30,0±4,0% больных; прогрессирование заболевания не зарегистрировано.*

Заключение: *Изучение молекулярно-генетических особенностей у 44 пациентов с В-клеточными НХЛ выявило ко-экспрессию мутационного гена c-myc и BCL 2 у 7 из 44 больных. Эти случаи отличались агрессивным течением болезни, «плохим» ответом на терапию, что предопределило применение высокодозной ПХТ с трансплантацией аутологичных стволовых клеток.*

Ключевые слова: *В-клеточная лимфома, мутационный ген c-myc, BCL 2, высокодозная полихимиотерапия с аутотрансплантацией ГСК.*