

PROGNOSTIC SIGNIFICANCE OF MEDIASTINAL MASS IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA CS II – CASE STUDY

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Diffuse large B-cell lymphoma with primary involvement of mediastinal lymph nodes is a separate nosological entity that should be distinguished from primary mediastinal large B-cell lymphoma. In most cases, DLBCL with primary involvement of the mediastinum has a poor prognosis.

International Prognostic Index IPI (age, Ann Arbor clinical stage, Eastern Cooperative Oncology Group (ECOG) performance status, serum LDH, extranodal involvement) and new R-IPI classify patients with DLBCL in certain risk groups and affect the choice of treatment.

Clinical stage II in case of patients with DLBCL does not stand for negative prognostic factor. However, the presence of bulky disease in these patients may affect subsequent treatment.

Patients with the same IPI risk may have a different response to the applied therapy. For that reason, today, the clinical IPI score must be considered along with biological factors or FDG-PET scan findings. *Acta Medica Medianae 2014;53(2):49-53.*

Key words: *mediastinal mass, prognostic significance, diffuse large B-cell lymphoma CS II*

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Introduction

Diffuse large B-cell lymphoma with primary involvement of mediastinal lymph nodes is a separate nosological entity that should be distinguished from primary mediastinal large B-cell lymphoma. In most cases, DLBCL with primary involvement of the mediastinum has a poor prognosis (1).

International Prognostic Index IPI (age, Ann Arbor clinical stage, Eastern Cooperative Oncology Group (ECOG) performance status, serum LDH, extranodal involvement) and new R-IPI classify patients with DLBCL in certain risk groups and affect the choice of treatment. The aforementioned R-IPI uses the same prognostic factors as IPI, but classifies patients into three risk groups and enables better prediction of disease outcome (2). Patients with the same IPI risk may have a different response to the applied therapy. For that reason, today, the clinical IPI score must be considered along with biological factors, such as Ki-67 proliferation index and Bcl-2. High IPI score and high percentage of Bcl-2+ and Ki-67 positive tumor

cells may represent poor prognostic factors that may help in detecting high-risk patients with DLBCL diagnosis (3). Application of rituximab in the treatment of DLBCL annuls the prognostic significance of molecular markers such as Bcl-2 and Bcl-6 (2).

Application of gene expression profiles points to the existence of three subtypes of DLBCL independent of the IPI (4). Given the high cost of such a methodology, it has been shown that common immunohistochemical analysis of the activated and differentiated DLBCL points to the existence of prognostically favorable GC and unfavorable non-GC (nGC) group. Research conducted by Trajkova et al. does not confirm the prognostic significance of GC and nGC phenotype (5). Shipp et al. present the analysis of gene profile expression with more than 6.000 genes in the diagnosis of DLBCL patients. DLBCL outcome is affected by NOR1, PDE4B and PKC beta regulating apoptotic response (6).

Prognostic significance of early 18F-fluoro-2-fluorodeoxyglucose positron emission tomography (18F-FDG PET) diagnosis has been confirmed by the study of event-free survival (EFS), resulting in three annual EFS in 46% of patients belonging to PET-positive group and 80% in the PET-negative group of patients (7).

Decreased absolute lymphocyte count (the number less than $0.84 \times 10^9/L$) in the diagnosis of non-Hodgkin lymphoma is an important prognostic factor for the overall survival (OS), event-free

survival (EFS) and the progression-free survival (PFS) (8).

Considering the aforementioned, the question arises as to which prognostic factors should be used when considering the presence of bulky disease as a prognostic factor of DLBCL CS II, in order to ensure proper selection of therapy.

Case report

We present a patient, PM, aged 29, whose symptoms began in 2010 with the occurrence of pricking chest pain and dry cough.

Objectively, the left supraclavicular lymph node can be palpated, the liver palpable one fingerbreadth.

Ph findings: The tumor grows diffusely or in the form of poorly specified nodules. It is made of large lymphoid cells that correspond to follicular center centroblasts and plenty of cells with light nuclei and conspicuous centrally located nucleoli corresponding to immunoblasts.

Immunophenotype: (CD20, CD79a)+, MUM1 -/+, Bcl6 -/+, (CD3, CD5, CD23, CD10, CD15, CD30, Bcl2)-, moderate proliferative activity of Ki-67 in approximately 30-40% of cells. The finding corresponds largely to LNH DLBCL post-germinal centroblast type.

Ultrasound examination of the neck verifies the existence of lymph nodes up to 10mm each and a left supraclavicular lymph node conglomerate 31x21 mm.

Heart ultrasound verifies a circular effusion around the heart muscle up to 16 mm, with no signs of cardiac tamponade. Pericardiocentesis evacuates 750 ml of serohemorrhagic effusion. Computerized tomography of the chest: In the front and middle mediastinum there is a large extensive inhomogeneous clearly limited mass (lymphoma).

Computerized tomography of the abdomen: Liver is enlarged and with homogeneous structure, with the right lobe of about 18 cm.

Bone marrow biopsy shows no elements of lymphoproliferative disorder.

The treatment is initiated with R-CHOP protocol (Amp Mabthera 750mg, Amp Vincristin 2mg, Amp Endoxan 1100mg, Amp Doxorubicin 95mg, Pronison tablets 100mg). After the second cycle, control computed tomography of mediastinum and ultrasound of the neck is performed, showing complete regression of lesions.

The patient received all of the planned eight cycles of R-CHOP polychemotherapy in March 2011. Assessing the efficiency of treatment in April 2011, the control MSCT of mediastinum registers the rest mass of an ovoid lymphoid infiltrate in front of ascending aorta 24x12 mm. PET scan performed in May 2011 shows the absence of binding radiopharmaceuticals in previously spotted retrosternal tumor mass. What is more, the zone of elevated glucose uptake in the sternum is spotted.

Repeated MSCT in November 2011 detects the presence of retrosternal soft tissue mass 36x54x102 mm in the upper and middle mediastinum, which homogeneously captures contrast. Repeated biopsy of the retrosternal tumor mass is performed.

With respect to relapse, the decision was made to continue the treatment with DHAP protocol (Amp Cisplatin 200 mg, AmpCytosar4gr, AmpDexamethason 1-4 days). After the second cycle of polychemotherapy by DHAP protocol, complete regression of the tumor mass of mediastinum was registered.

Discussion

Mediastinal mass is a predictor of the future course of the disease of certain lymphomas. Involvement of mediastinum exists in all subtypes of lymphoma, and the most common are the following: classical Hodgkin lymphoma (cHL) – nodular sclerosis, non-Hodgkin lymphoma (NHL) diffuse large B-cell lymphoma (DLBCL), primary mediastinal lymphoma with sclerosis (PMBL) and T-lymphoblastic lymphoma (9).

In case of Hodgkin's lymphoma, mediastinal mass greater than one third of the chest is still a more important determinant of further disease prognosis than the Ann Arbor staging or clinical prognostic factors (10). The negative prognostic significance of mediastinal mass also exists in case of T-lymphoblastic lymphoma (11). In patients with PMBL, mediastinal mass greater than 10cm is not a significant predictor of survival, as stated by Asraf et al. in their research (12).

Bulky disease does not affect the outcome of the disease in patients with DLBCL and does not give rise to the application of radiotherapy, as stated by Phan et al. in their research. Patients have had equal benefit from the application of radiotherapy, regardless of the presence of bulky disease. The aforementioned authors state that the value of the standardized PETSUV input, Ki-67 and bulky disease do not affect the overall survival (OS) and the period with no recurrence (PFS) if studied separately. Given that the aforementioned prognostic factors indicate aggressive course of the disease, all three factors have been considered together as a triple positive or negative finding (13).

The patient in question is in the CS IIB with involvement of the mediastinum. The patient belongs to the group of medium-high risk group based on aaIPI. Based on the R-IPI Prognostic Index, the patient belongs to a group with a good prognosis.

The treatment is carried out on the basis of ESMO recommendations for patients younger than 60 years old belonging to medium high-risk group. The treatment includes all 8 cycles of R-CHOP protocol (14).

The application of computed tomography of mediastinum, followed by PET scan in the assessment of the disease after the therapy based on 8 cycles of R-CHOP points to the presence of a retrosternal tumor mass and the absence of binding radiopharmaceuticals.

Current recommendations of the National Comprehensive Cancer Network (NCCN) support the implementation of three R-CHOP cycles with involved field radiotherapy (IFRT) in early stages without the presence of bulky disease. These recommendations also allow the application of 6 to 8 R-CHOP cycles with or without IFRT in case of the presence of bulky disease (15).

The patient was not treated with radiotherapy whose position and role were investigated in the studies conducted in pre-rituximab era and later at the time of its application.

The use of rituximab treatment in patients in the early stages of DLBCL has been investigated in studies such as SWOG or MinT, which show equal efficiency of the application of rituximab in the early stages of DLBCL in relation to the use of radiation therapy (16).

In the case of the aforementioned patient, the finding of FDG-PET scan after the applied therapy patient shows the absence of binding radiopharmaceutical. The relapse of the disease was identified after repeated biopsy of retrosternal tumor mass in 2011.

Some studies address the importance of application of 18F-FDG PET/CT before the end of treatment with chemotherapy, after 2 or 4 cycles of therapy, as well as the importance of early changes in treatment modalities. Unfortunately, there is no evidence that early changes in therapy based on the findings of 18F-FDG PET/CT affect the survival of patients (17).

Despite significant effectiveness of R-CHOP in the first-line treatment, disease relapse has occurred. The standard in the treatment of relapse

is reflected in the application of high-dose chemotherapy (DHAP, ESHAP, mini-BEAM and ICE) and autologous hematopoietic stem cell transplantation. Further treatment has involved the application of DHAP protocol, so that the patient received four cycles of this protocol prior to autologous bone marrow transplantation (18).

Prognostic factors affecting further course of treatment of patient with relapsed DLBCL have been reflected in patient's chemosensitivity, the duration of the initial remission of less than 12 months, the presence of bulky disease at the time of HSCT (19). Moderate proliferative activity of Ki-67 and the negativity of Bcl-2 with medium-high aaIPI have been the favorable prognostic factors for the further course of the disease.

Application of DHAP protocol has resulted in complete regression of the tumor mass of mediastinum and complete remission of the disease. After that, autologous hematopoietic stem cell transplantation has been performed, resulting in remission of the underlying disease.

Conclusion

In patients with DLBCLCSII, mediastinal mass maybe prognostically significant if considered together with the biological prognostic factors and the FDG-PET scan findings.

The presence of mediastinal mass in this case report has been accompanied by a moderate proliferative index Ki-67 at the time of disease presentation and the absence of binding radiopharmaceutical after 8 cycles of R-CHOP on the FDG-PET scan.

In the case report, mediastinal mass was not a negative prognostic factor. After the identified relapse, the patient received 4 cycles of DHAP protocol, after which the autologous hematopoietic stem cell transplantation was performed and the disease remission achieved.

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PROGNOSTIČKI ZNAČAJ MEDIJASTINALNE MASE KOD BOLESNIKA SA DIFUZNIM B KRUPNOĆELIJSKIM LIMFOMOM U DRUGOM KLINIČKOM STADIJUMU - PRIKAZ BOLESNIKA

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Difuzni B krupnoćelijski limfom (DBKL) sa primarnim zahvatanjem medijastinalnih limfnih nodusa poseban je nozološki entitet, koji treba razlikovati u odnosu na primarni medijastinalni krupnoćelijski B limfom. U većini slučajeva, DBKL sa primarnim zahvatanjem medijastinuma ima lošu prognozu.

Internacionalni prognostički indeks (IPI) (starost, Ann Arbor klinički stadijum, Eastern Cooperative Oncology Group (ECOG) performance status, serumska LDH, ektranodalna zahvaćenost) i novi R-IPI klasifikuju bolesnike sa DBKL u određene grupe rizika i utiču na izbor lečenja.

Drugi klinički stadijum kod bolesnika sa DBKL ne predstavlja negativan prognostički faktor, ali prisustvo voluminozne bolesti može kod ovih bolesnika uticati na dalje lečenje.

Bolesnici sa istim IPI rizika mogu imati različit odgovor na primenjenu terapiju. Zato se danas klinički IPI skor mora razmatrati zajedno sa biološkim i nalazom FDG-PET skena. *Acta Medica Medianae 2014;53(2):49-53.*

Ključne reči: medijastinalna masa, prognostički značaj, difuzni B krupnoćelijski limfom, drugi klinički stadijum