

PRIMARY MEDIASTINAL B LARGE CELL LYMPHOMA - CASE REPORT

Irena Čojbašić

Primary mediastinal large B cell lymphoma (PMLBCL) has been recognized as a specific subtype of diffuse large B cell lymphoma with characteristic clinical, pathological and biological features.

This paper presents a diagnostic and therapeutic approach in the treatment of patient with this disease. A patient aged 35 years visited a doctor because of the presence of B-symptoms and signs of the existence of superior vena cava syndrome. After the transbronchial biopsy of the tumor mass, the diagnosis PMLBCL was established. This case has been regarded as localized stage lymphoma with medium risk. The patient received induction therapy by R-MACOP-B protocol and achieved a clinical response of partial remission type. After that, radiotherapy of mediastinum was carried and salvage therapy was applied but no further reduction in tumor mass was observed. Treatment was continued by the application of autologous hematopoietic stem cell transplantation. Control PET/CT scan showed the absence of a viable tumor, thus it was concluded that clinical response of complete remission type was achieved.

The optimal therapeutic approach in the treatment of patients with PMLBCL remains a matter of debate. The use of a therapeutic protocol MACOP-B in combination with mediastinum radiotherapy has been demonstrated to improve disease-free survival, while the importance of additional treatment with rituximab and the role of PET scan in the assessment of therapeutic response continue to be reviewed. *Acta Medica Medianae 2014;53(3):46-53.*

Key words: primary mediastinal large B cell lymphoma, chemotherapy, radiotherapy, combined modality treatment, response rate

Clinic of Hematology and Clinical Immunology, Clinical Center Niš,
Niš, Serbia

Contact: Irena Čojbašić
Clinic of Hematology and Clinical Immunology
Clinical Center Niš
Boulevard Zorana Đinđića 48, 18000 Niš, Serbia
E-mail: icojbasic@gmail.com

Introduction

Primary mediastinal large B cell lymphoma (PMLBCL) is recognized as a subtype of diffuse large B cell lymphoma (DLBCL) by the Revised European-American classification of lymphoid neoplasms (REAL) and the World Health Organization (WHO) classification, on the basis of the unique morphology, the place of presentation of disease and the clinical behavior (1,2). It belongs to a group of rare entities and occurs in approximately 10% of all diffuse large B cell lymphomas. Patients are usually young women, in the third and fourth decade of life with a large mediastinal mass, with frequent involvement of intrathoracic structures.

Pathologically, this type of tumor is characterized by diffuse proliferating large cells with clear cytoplasm and presence of the variable degree of

sclerosis. Immunohistochemical analysis shows the presence of B cell CD19, CD20, CD22 and CD79 antigens in all cases. The expression of Bcl-2 is present in 80%, the CD10 expression is low, while the CD21 and CD15 are negative in all cases. The expression of surface immunoglobulin is negative and expression of HLA molecules of class I and II is low to absent. In more than half of the cases the Bcl-6 gene mutation and functional IGH somatic mutations are demonstrated, indicating that the origin of lymphoma cells are postgerminal center cells or activated germinal center (3-5).

In most patients with this disease the only place of lymphoma infiltration is mediastinum. However, lymphoma can spread locally seizing other organs and structures of the chest, which is manifested by symptoms such as dyspnea, cough, chest pain and obstruction of the superior vena cava. Bulky mediastinal mass is present in the 60%-70%, while intrathoracic spread to adjacent organs is present in 50% of patients. At the time of diagnosis, only 20% of patients are in the CS III-IV and extranodal dissemination or infiltration of bone marrow is rare. B symptoms are frequently present and 30-40% of patients have signs of superior vena cava syndrome.

Clinically, PMLBCL is aggressive lymphoma and its relative response to treatment is controversial. It is believed that the initial treatment is of particular importance in the treatment of PMLBCL because salvage therapy for refractory disease or relapse is of the limited efficacy. The choice of initial chemotherapy/immunochemotherapy and the potential benefits of applying high-dose therapy in first remission is still a matter of debate. Also, the role of consolidation mediastinum radiotherapy is yet to be confirmed.

Case report

Patient D.K. 35 years old, contacted his physician, having the signs and symptoms such as night sweats, weight loss and fever, which he had a year before. Problems like shortness of breath, coughing and chest pain he felt for a month before. In clinical trials the absence of peripheral lymphadenopathy and palpable hepatosplenomegaly were noticed, as well as the presence of signs of superior vena cava syndrome as a dyspnea and also emphasized venous images of the thorax. Personal and family history were unremarkable. Chest X-ray showed an abnormal cardiomeastinal silhouette, caused by large central mediastinal mass extending within the superior hemithorax medially (Figure 1).

Computed tomography (CT) of the chest revealed a tumor mass in the anterior mediastinum of size of 12.5×8.7cm. Tumor mass was spreading craniocaudal and was covering the entire retrosternal space, pushing the heart and trachea backwards. Pathologically enlarged lymph nodes were not observed and there was no free liquid in the thorax (Figure 2).

For the purpose of diagnosis, bronchoscopy and transbronchial biopsy of the tumor mass were performed. The histopathological examination with the immunohistochemistry showed that the tumor cells were: EMA, CK, CK7-, TTF, CEA, CD79b+, CD20+, CD3-CD5-, CD43-, CD45RO-, CD10-, bcl-2 + bcl -6 -, MUM-1 +, CD38-, CD23-. Proliferative activity was high, over 60% of tumor cells were clearly Ki-67+. According to its morphology, immunohistochemical characteristics, mode of growth and localization, tumor was most probably PMLBCL. Laboratory testing was conducted. Complete blood count showed: WBC

8,4

40,3L/L, PLT 358 analysis was in the referential values except for an increase in non-specific inflammatory parameters: SE 70, LDH 1194U/L, CRP 103,3mg/L. Immunology, electrophoresis and immunoelectrophoresis protein levels were within the reference values. Abdominal ultrasound showed the absence of hepatosplenomegaly and lymphadenopathy in the abdomen. In order to assess the extent of disease, a bone marrow biopsy was

performed and showed a hyper-cellular bone marrow with no evidence of lymphoid cells infiltration.

The patient was diagnosed as: PMLBCL CS IIB-b (bulky disease) by the Ann Arbor classification, IPI score of 2, ECOG 2. Therapeutic options were considered, especially the application of R-EPOCH protocol, but in line with the recommendations of the national guidelines it was decided to carry out the treatment of R-MACOP-B protocol for 12 weeks. Treatment was followed by complications such as the development of herpes zoster infection. After treatment, the evaluation of therapeutic response was conducted. Repeated CT scan of the chest showed a reduction of size of the mediastinal tumor mass (6.6×8.4×6.6cm) and also a positive biochemical parameters of blood were registered, which was understood as a partial remission of disease (Figure 3).

Given that there was a partial response to chemotherapy, radiotherapy of mediastinum was applied (TD 45Gi/26 sessions). After radiotherapy, the control CT of the chest showed no reduction in tumor mass in the mediastinum (5.0×7.6×9.2cm). Further treatment was continued by application of salvage therapy via ESHAP protocol. Evaluation after 4 cycles showed the presence of a tumor mass of the same size (5.8×7.0×9.5cm), as shown in Figure 4.

We performed a revision of histopathological findings and confirmed the diagnosis of PMLBCL. The result of repeated bone marrow biopsy and B-monoclonality of bone marrow lymphocytes were both within normal limits. PET/CT scan of the whole body was performed by injection of fluoro-deoxyglucose labeled fluorine-18 (FDG). In PET sections 3 small areas of increased accumulation of FDG (SUVmax 4.4 to 6.0) were present, in the projection of larger soft-tissue mass in the anterior mediastinum, which was noticeable by the CT. In the rest of the body the accumulation of FDG was within the normal limits (Figure 5).



Figure 1. Chest X-ray in PA; enlarged mediastinal shadow

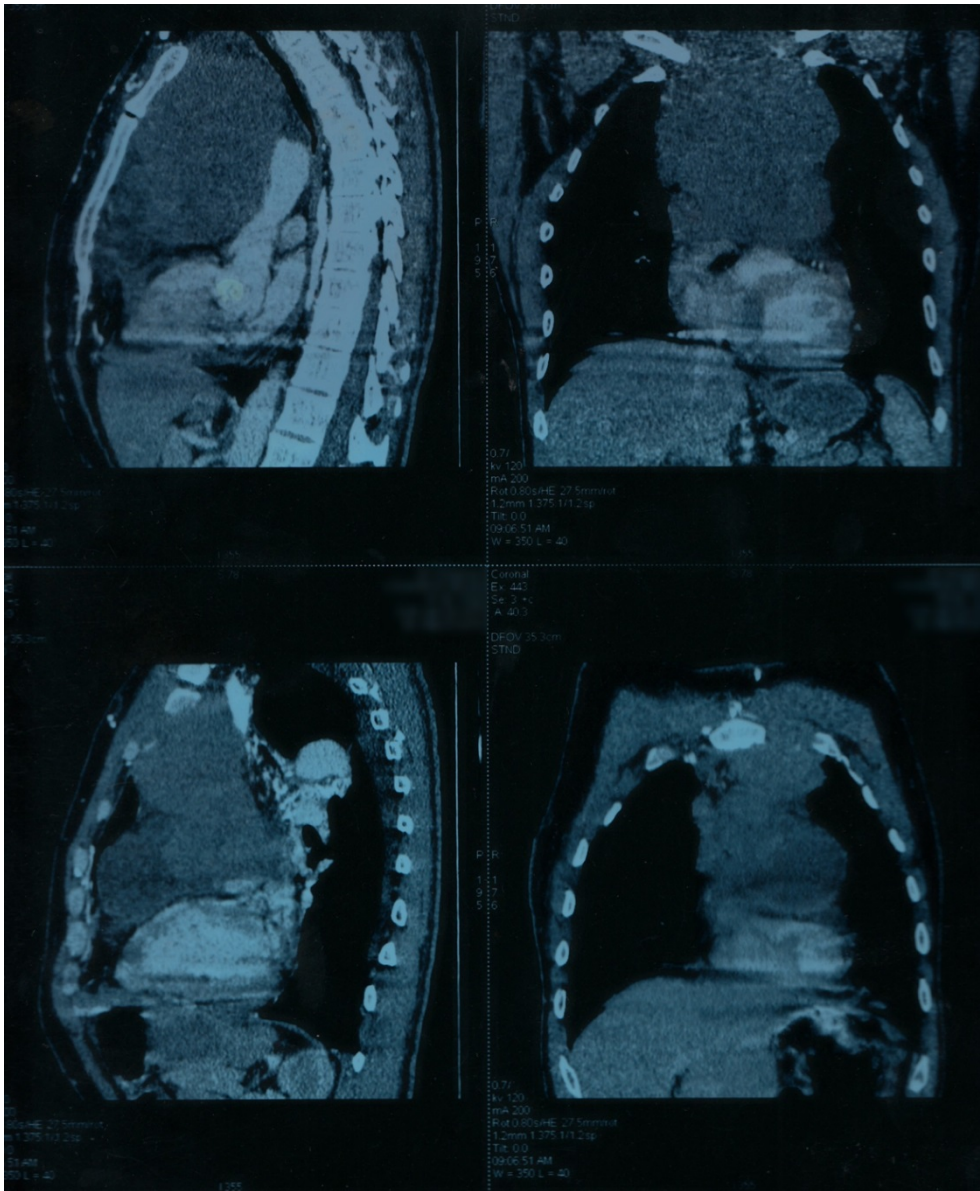


Figure 2. CT of the mediastinum; large soft tissue tumor changes in the anterior mediastinum

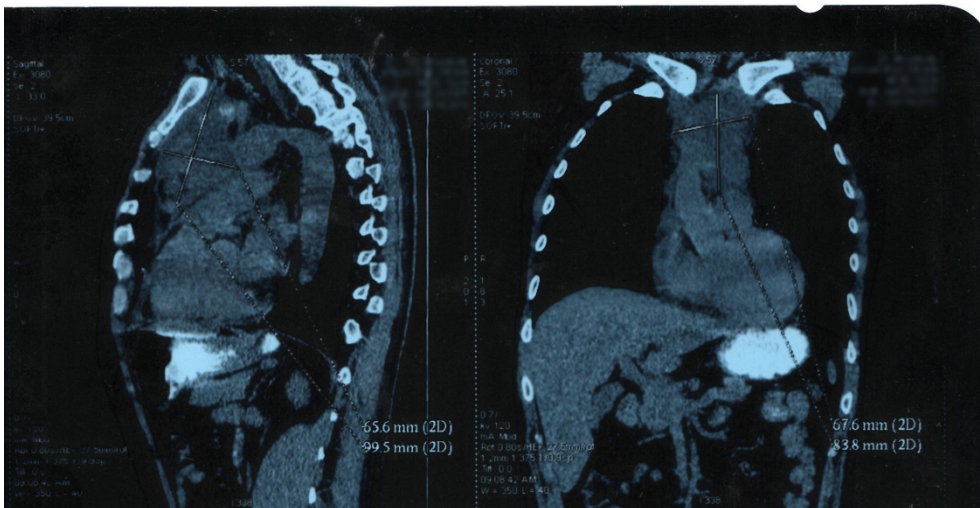


Figure 3. CT chest after initial chemotherapy; reducing the size of the mediastinal mass

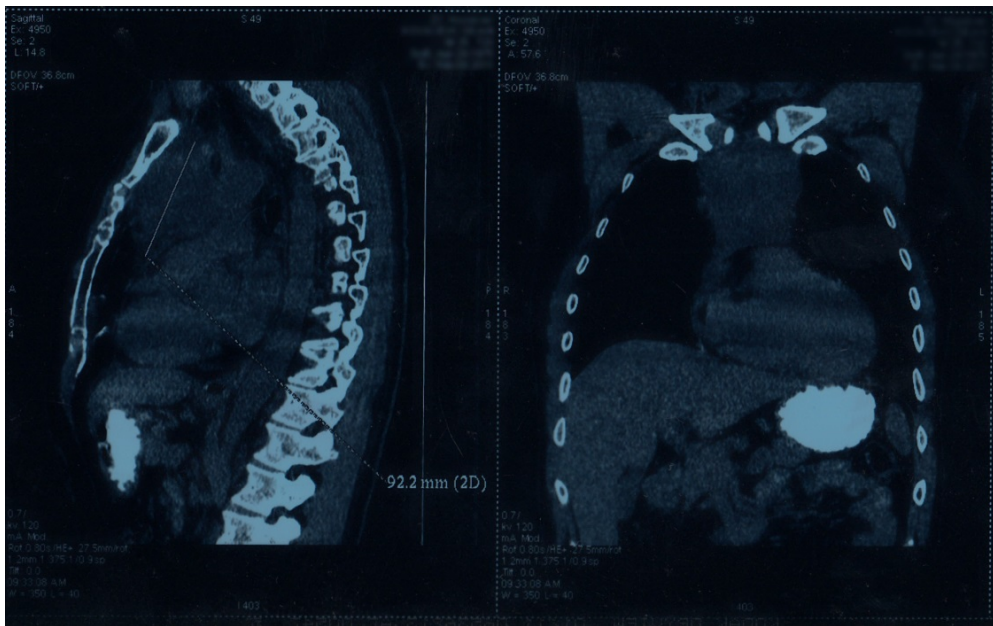


Figure 4. CT chest after radio and salvage therapy; persisting tumor mass in the mediastinum of the same size

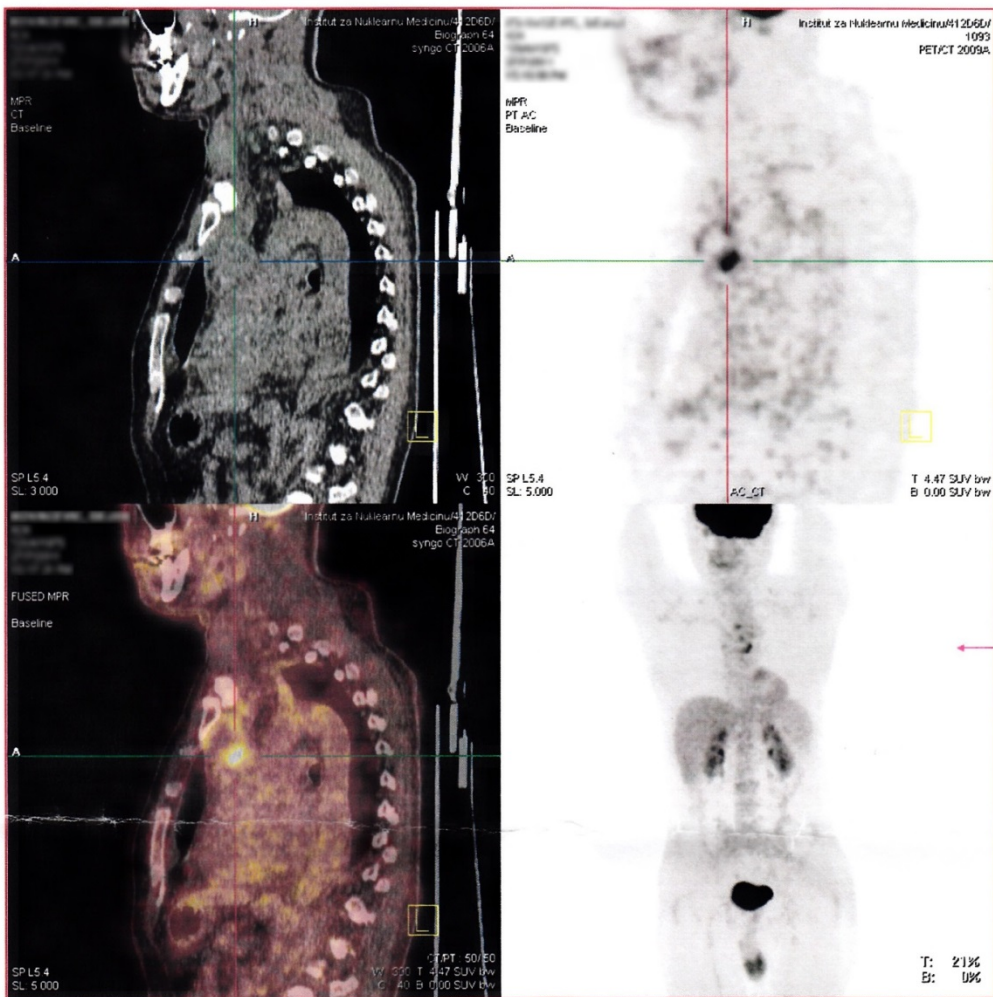


Figure 5. PET/CT scan of the chest after chemotherapy and radio therapy; soft tissue formation in the mediastinum within which three small moderately active zones were observed

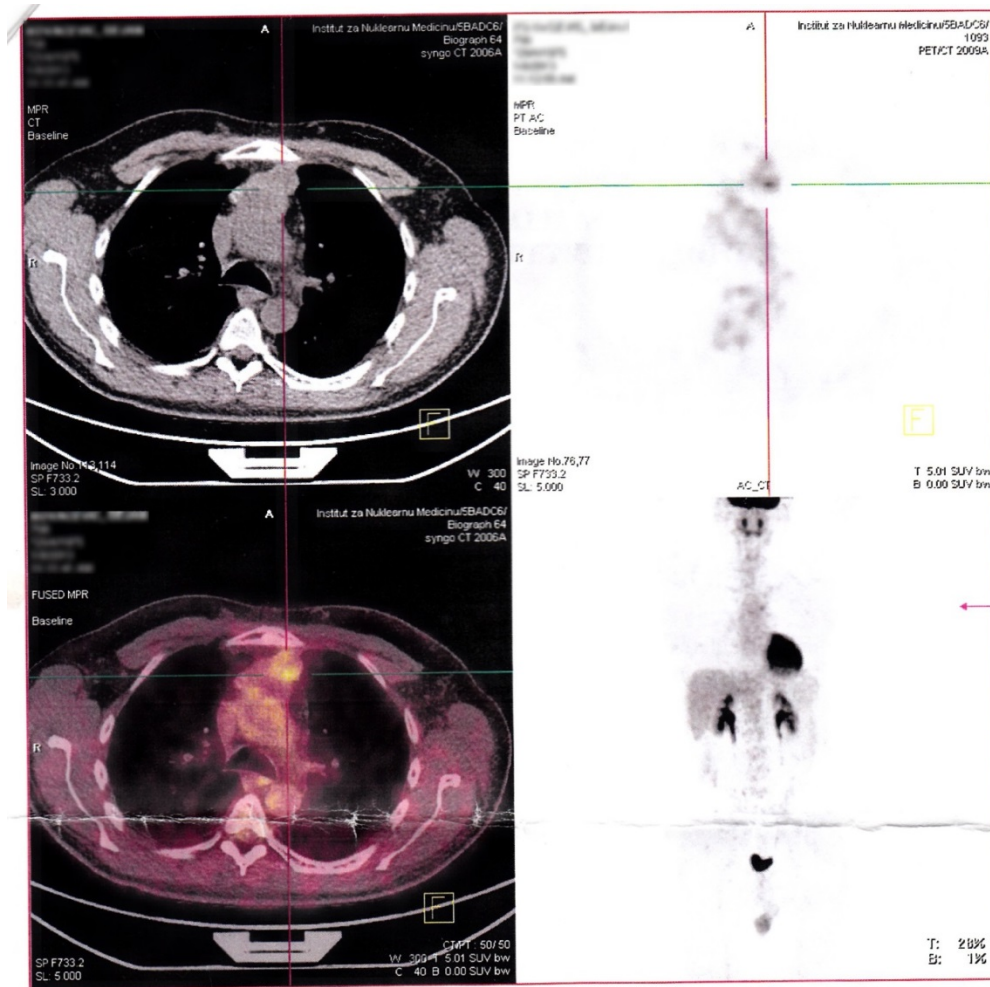


Figure 6. PET/CT scan of the chest after ASCT; without the presence of viable lymphoma tissue

Considering that the earlier therapy did not provide satisfactory clinical response, it was decided that further treatment was continued by the application of autologous stem cell transplantation (ASCT). Considering the age, nature and course of the disease, as well as some chemosensitivity manifested, it was consultatively agreed that the application of high-dose chemotherapy by protocol ESHAP with addition of granulocyte-colonostimulating factor (G-CSF) should have been applied in order to collect autologous peripheral stem cell. Autologous stem cell transplantation was performed in three stages. Pretransplant phase consisted of placing the CVC and the implementation of procedures of prevention of tumor lysis syndrome, mucositis and possible infections. Conditioning was conducted using the BEAM therapy protocol. During the phase of transplantation the patient received 6×10^8 HSCs/kg of body weight. Procedure of myeloablation passed properly. In posttransplant phase haematological recovery occurred on the tenth day, as it was confirmed by analysis of the myelogram on the thirteenth day following ASCT. There were no serious complications related to transplantation. Result of PET/CT after ASCT

showed that in contrast to previous findings in the anterior mediastinum there were only two small discrete areas of increased take-over of FDG (SUV up to 2.7 paratracheal) in the absence of viable tumor, as shown in Figure 6.

During the patient follow-up, results of the control PET/CT scans, which were performed every 6 months, showed that there was no presence of the viable tumor. At the last PET/CT scan, which was done 2 years after ASCT, increased metabolic activity in the soft tissue changes in the anterior mediastinum was registered, with some fluctuations but with no clear progression. In other shown parts of the body, FDG distribution was within the normal range. Monitoring indicates that the patient is still alive and without the presence of the signs of disease.

Discussion

Optimal treatment of PMLBCL is still under discussion, although some studies suggest better treatment outcome with high-dose chemotherapy regimens, while the role of radiotherapy remains poorly defined. Early experiences in treating

PMLBCL showed that the use of a CHOP protocol (cyclophosphamide, doxorubicin, vincristine, prednisone) had worse results in terms of event-free survival and overall survival compared to the use of high-dose chemotherapy with ASCT (6). Later studies have shown that application of B-MACOP protocol (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) demonstrates a trend towards a superior outcome of PMLBCL patients, as compared to application of CHOP protocol (7,8). Better treatment results were achieved by combined treatment with the application of intensive chemotherapy of MACOP-B protocol in the first line, with mediastinal involved field radiotherapy, which induces a high response rate and a high rate of disease-free survival (9-11). Large multinational study compared the outcome of patients with PMLBCL with sclerosis after administration of the first-generation regimen (CHOP), regimen of the third generation (MACOP-B) or high-dose chemotherapy (HD/ASCT). The final rate of complete remission was achieved in 61% with CHOP protocol, 79% of MACOP-B protocol and 75% with HD/ASCT, while the rate of the projected 10-year overall survival was 44%, 71% and 77%, respectively (12). There is few clear evidence that are needed to quantify the significance of the addition of rituximab to chemotherapy for PMLBCL, although its application is now widely adopted based on the results of treatment of DLBCL (13,14). Addition of rituximab to chemotherapy protocol EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in patients with PMLBCL led to a significant improvement in event-free survival and overall survival (15), while there was no obvious advantage in terms of survival after rituximab was added to the CHOP protocol, or it was similar when R-CHOP was compared to MACOP-B protocol (8).

Low incidence of bone marrow infiltration by lymphoid cells and relatively young age of the patients with PMLBCL led to the consideration of the application of high-dose chemotherapy and ASCT for the consolidation of first remission. Results of GEL-THERE registry showed that after prolonged monitoring of patients with PMLBCL, those presenting with high-risk characteristics at diagnosis or have achieved partial remission to induction therapy, with the application of ASCT have better overall survival of 77% after 10 years (16). The effectiveness of early intensification treatment integrating chemotherapy, ASCT and radiotherapy in patients with high risk PMLBCL, resulted in achievement of disease-free survival of 93% after a mean follow-up of 3 years (17). The role of the consolidation radiotherapy was clearly confirmed in IELSG study which showed that many patients, who achieved a partial remission after completion of the chemo-

therapy, could achieve a complete remission by receiving radiotherapy (12). Mazzaratto et al. (18) showed the results of their study in which, after induction chemotherapy, 42% of patients were in complete remission and this percentage increased to 95% after radiotherapy. Considering the significant long-term toxicity of radiation, re-examination of the role of radiotherapy is needed, especially now that rituximab has become an integral part of therapy for PMLBCL.

Because of the existence of the significant fibrosis component in this type of lymphoma, residual mediastinal mass is often present after the completion of therapy. Therefore, it is necessary to make a difference between those who have residual disease and those with fibrous tissue. PET/CT scan has proved useful in identifying patients with Hodgkin's and aggressive non-Hodgkin's lymphoma that will probably relapse. Several studies have confirmed that PET-positivity after induction therapy is very predictive for the presence of residual disease, while PET-negativity strongly suggests the absence of active disease, but the histopathological verification is important in patients who show PET-positivity (19,20).

According to international guidelines for the recommended treatment of PMLBCL, MACOP-B application protocol in combination with the mediastinal radiotherapy is recommended. In addition, the impact of adjuvant therapy with rituximab and the role of PET scan is still questioned because of reported controversial results. By the introduction of PET/CT, scan-guided radiotherapy after immunochemotherapy provides patient-tailored therapeutic strategy that reduces the use of radiotherapy and maintains clinical outcome. Moreover, results of recent studies have shown that additional treatment with rituximab does not change the final results of achieving complete remission and survival without disease using MACOP-B protocol (21,22).

Conclusion

By the overall treatment of primary mediastinal large B cell lymphoma in our patient, a complete remission was achieved. Therapeutic decisions were followed by dilemmas, from the optimal approach regarding the choice of the induction protocol in relation to the achieved efficiency and potential toxicity, over the role of applied salvage protocol with high-dose chemotherapy with ASCT in achieving complete remission, to determination of the optimal monitoring rate of achieved therapeutic response. Prospective studies are necessary to assess the best system therapy for PMLBCL in an era of rituximab, as well as to reexamine the role of radiotherapy in the treatment of this disease.

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PRIMARNI MEDIJASTINALNI B KRUPNOĆELIJSKI LIMFOM - PRIKAZ BOLESNIKA

Irena Čojbašić

Primarni medijastinalni krupnoćelijski B limfom (PMLBCL) prepoznat je kao specifičan podtip difuznog krupnoćelijskog B limfoma, sa karakterističnim kliničkim, patološkim i biološkim osobenostima.

U ovom radu prikazan je dijagnostički i terapijski pristup u lečenju bolesnika sa ovom bolešću. Bolesnik star 35 godina javio se lekaru zbog prisustva B-simptoma i sa znacima postojanja sindroma vene cave superior. Nakon izvršene transbronhijalne biopsije tumorske mase, postavljena je dijagnoza PMLBCL. Stadiran je kao lokalizovani stadijum limfoma sa srednjim stepenom rizika. Bolesnik je primio indukcionu terapiju po R-MACOP-B protokolu i postigao klinički odgovor tipa parcijalne remisije. Nakon toga je sprovedena radioterapija medijastinuma i primenjena salvage terapija, ali bez daljeg smanjenja tumorske mase. Lečenje je nastavljeno primenom autologne transplantacije matičnih ćelija hematopoeze. Kontrolni PET/CT sken pokazao je odsustvo vijabilnog tumora, tako da je konstatovano postizanje kliničkog odgovora tipa kompletne remisije.

Optimalan terapijski pristup u lečenju bolesnika sa PMLBCL i dalje je predmet rasprave. Primena terapijskog režima MACOP-B u kombinaciji sa radioterapijom medijastinuma dokazano poboljšava preživljavanje bez bolesti, dok se značaj dodatne terapije sa rituksimabom i uloga PET skena u proceni terapijskog odgovora i dalje preispituju. *Acta Medica Medianae 2014;53(3):46-53.*

Ključne reči: primarni medijastinalni krupnoćelijski B-limfom, hemioterapija, radioterapija, kombinovani modaliteti lečenja, stopa odgovora