Original Paper

Therapeutic Options in Diffuse Large B-Cell Lymphoma - A Retrospective Study and Review of the Literature

ANA-MARIA PATRASCU[1], JANINA NACEA[1], Ş. PATRASCU[2], A. GOGANAU[2], FLORENTINA DELCEA[3], L. MOGOANTA[4], IONELA ROTARU[1]

[1]*Department of Hematology, University of Medicine and Pharmacy of Craiova, Romania*

[2]*Department of Surgery, University of Medicine and Pharmacy of Craiova, Romania*

[3]*Department of Dermatology, Emergency County Hospital of Slatina, Romania*

[4]*Department of Histology, University of Medicine and Pharmacy of Craiova, Romania*

ABSTRACT: The aim of this retrospective study was to assess the differences between standard R-CHOP and other Rituximab-associated chemotherapy (R-miniCHOP and R-CHOEP) regimens in terms of survival and potential adverse effects. The six-month survival outcomes of 94 diffuse large B-cell lymphomas (DLBCL) patients indicated no statistical difference between overall survival and disease-free survival in the two subgroups. The biological response to therapy (blood count, LDH levels) was similar in both subgroups. Despite having different clinical indications, R-miniCHOP and R-CHOEP provide viable therapeutic alternatives to the standard R-CHOP regimen.

KEYWORDS: *diffuse large B-cell lymphoma, prognosis, CHOP, rituximab*

Introduction

Despite being considered the most frequent type of non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL) is in fact a heterogenous group of lymphoproliferative disorders, with different clinical, morphological, immunohistochemical and genetic features [1]. The importance of these particularities lies in their potential role in the selection of the optimal therapeutic algorithm, as well as individualized predictors for the efficiency of the selected regimen. The treatment protocol, on the other hand, did not change much during the last twenty years. One notable exception was the introduction of Rituximab as an important addition to standard chemotherapy protocol in CD20+ cases, providing significant improvement in complete remission rate, disease-free survival and overall survival, with minimal added toxicity [2].

Nevertheless, up to 15% of patients diagnosed with DLBCL exhibit primary refractory disease and 20-25% relapse after the initial response to R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) regimen [2]. Therefore, other therapeutic solutions were to be tested, such as R-miniCHOP (consisting of adjusted short-term R-CHOP regimen), and R-CHOEP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Etoposide and Prednisone), which adds Etoposide to the conventional regimen. The indication for each of these therapies usually depends on a series of factors, such as age, stage of the disease and biological status, but no precise recommendation has been made so far, as there is only a limited number of studies addressing this issue [3-5].

The aim of this study was to evaluate three Rituximab-based treatment regimens in DLBCL according to their short-term biological impact, overall and disease-free survival rate, as well as to perform a detailed literature review of the current therapeutic options in DLBCL according to the Ann Arbor classification and the 2015 ESMO Clinical Practice guidelines.

Methods

We performed a ten-year retrospective analysis of all de novo patients with DLBCL admitted and treated in the Clinical Department of Hematology, at Filantropia City Hospital of Craiova. One hundred and twenty-eight DLBCL cases were diagnosed and classified according to the 2008 World Health Organization classification of tumors of hematopoietic and lymphoid tissues [6]. We selected all DLBCL-confirmed patients that followed Rituximab-based chemotherapy. Only those cases undergoing the complete therapeutic protocol were included. The protocol of our study was approved by the Ethics Committee of the

University of Medicine and Pharmacy of Craiova.

Data analysis was performed with GraphPad Prism v7.0 (GraphPad Software Inc. San Diego, USA). Data was analyzed by descriptive statistics and survival estimates using the Kaplan-Meier method. The comparative analysis of the survival endpoints was performed by the Mantel-Cox and Wilcoxon regression tests. Statistically significant results entailed the *p* value inferior to 0.05 limit in both tests.

Results

Ninety-four patients were selected according to the inclusion criteria. The following regimens were used: R-CHOP, R-CHOEP, and R-miniCHOP. Mean age in the R-CHOP group was 53.2 years, while in the alternative rituximab-based regimen (R-CHOEP and R-miniCHOP) was 66.5 years.

The patients were divided in two groups, both including Rituximab as an indispensable therapeutic agent. The first group of 78 cases was treated with R-CHOP regimen, while the second group, consisting of 16 cases, included all patients with other Rituximab-associated regimen, such as R-miniCHOP and R-CHOEP.

Relevant blood test analysis indicated variations of their mean values at different timeframes (T0-the beginning of therapy, T1-end of therapy/6 months). However, no statistical difference was observed between the groups.

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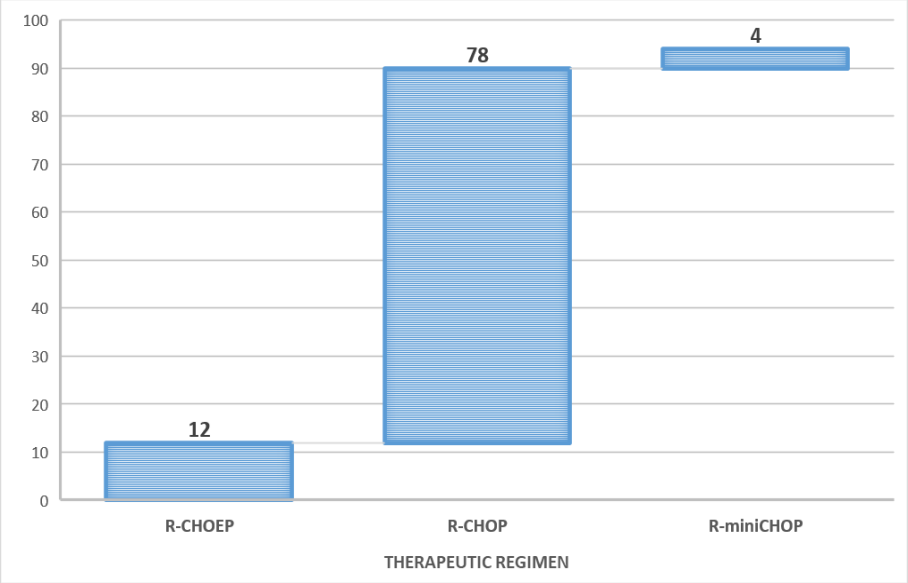

Fig. 1. Patients distribution according to DLBCL treatment regimen

Table 1. Variation of statistical parameters of hemoglobin, lymphocytes and LDH values at the beginning of therapy (T0) and at 6 months/end of therapy (T1)

	Mean	*Std. dev.*	*Median*	*Var.*	*Min/Max*	*SEM*	*95% CI*	*p value: t-test, Welch correction*
Hb (T0)	11.8	2.164	12.2	18.34	7.8/16.9	0.48	10.78-12.81	0.66
Hb (T1)	12.08	2.106	12.1	17.44	6.8/17.52	0.52	10.95-13.2	
Lymphocytes (T0)	1842	942.5	1620	51.16	389/3750	228.6	1358-2327	0.356
Lymphocytes (T1)	1563	686.2	1300	43.9	590/3150	190.3	1148-1978	
LDH (T0)	420.4	153.6	359	36.53	273/733	51.19	302.4-538.5	0.3375
LDH (T1)	343.9	227.9	240	66.28	124/827	58.86	217.7-470.2	

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The comparative analysis of the Kaplan-Meier curves in the two groups indicated no statistical difference regarding the 5-year overall survival (Mantel-Cox test: p=0.47; Gehan-Wilcoxon test: p=0.44), with an average survival rate of 43.36% in the R-CHOP group, and 35.15% in the second group. (Fig. 2)

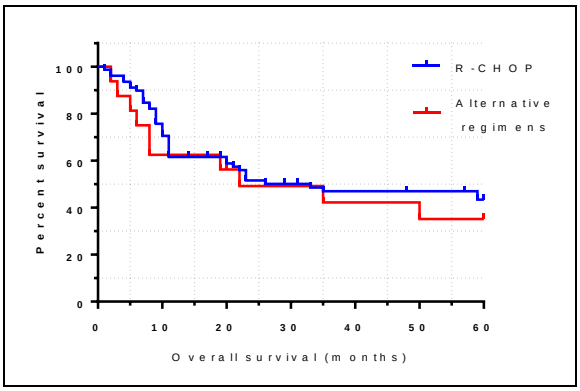

Fig. 2. Overall survival for R-CHOP vs. alternative Rituximab-based regimens in DLBCL patients

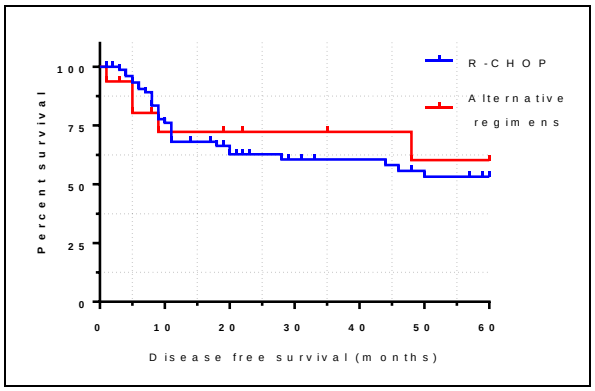

Fig. 3. Disease-free survival for R-CHOP vs. alternative Rituximab-based regimens in DLBCL patients

When disease-free survival was analyzed similar results were observed. There was no statistical difference between the R-CHOP and the alternative Rituximab-based regimens (Mantel-Cox: p=0.79; Gehan-Wilcoxon: p=0.94). The mean survival rate in the first group was 53.18%, and 60.26% in the second group. (Fig. 3)

Discussion

The therapeutic options in diffuse large B-cell lymphoma witnessed minimal changes during the last two decades. Immunotherapy, along with anti-CD 20 monoclonal antibody Rituximab, provided the most significant therapeutic breakthrough of the last few years. Due to the progress made over the last decades in terms of pathogenic and molecular heterogeneity of this disease, new regimens and therapeutic agents are being developed in order to improve the results normally achieved with conventional treatments. The treatment of lymphomas evolves towards targeted therapies, by understanding tumor biology and discovering new signaling pathways. Moreover, several biological therapies are available today, ranging from the already known interferon therapy, to rituximab or radiolabeled antibodies, to name just a few of the recent acquisitions in the DLBCL therapeutic armamentarium [7].

The management of DLBCL is distributed into several categories according to the stage of the disease, organ involvement, age and relapse after initial remission [8]. The 2015 ESMO guidelines provided a further patients' distribution according to the International Prognostic Index (IPI) score.

Therefore, in young low-risk patients without a bulky mass six cycles of CHOP, combined with 6 cycles of Rituximab every 21 days are recommended as the standard treatment in stage I and II CD20+ DLBCL. For young low-intermediary risk patients with bulky disease, the treatment regimen consists of six R-CHOP cycles every 21 days along with localized radiotherapy, or the more intensive R-ACVBP (Rituximab, Doxorubicin, Vindesine, Cyclophosphamide, Bleomycin and Prednisone) regimen every 14 days, without radiotherapy. For young high or intermediary-high risk patients either 6-8 CHOP and Rituximab chemotherapy cycles every 21 days, or more intensive regimens such as R-ACVBP, R-CHOEP can be used [9,10].

For older patients (between 60 and 80 years old) the ESMO guidelines recommend 6 to 8 cycles of R-CHOP every 21 days. Local radiation therapy in older patients with bulky disease seems to be efficient. For patients aged over 80 years R-miniCHOP is advised. In case of cardiac involvement or other co-morbidities, Doxorubicin can be withdrawn from the regimen or it can be substituted by Gemcitabine, Etoposide or liposomal Doxorubicin [9,10].

Apart from the risk stratification, another important landmark in DLBCL treatment is the extension of the disease. Stage I and II lymphoma without bulky disease is found in some 30% of DLBCL. Initially, patients have been treated by localized radiotherapy with good short-term results, but remission could not be maintained in the long term for most of the cases [11]. Nowadays, patients with localized disease but without bulky mass are good candidates for

chemotherapy, with standard treatment for these cases consisting of 6 R-CHOP cycles every 21 days [11].

Several studies compared the advantages of associated chemo- and radiation therapy over chemotherapy alone, with conflicting results. While some authors plead for the associated therapy, most papers did not observe any substantial benefit for localized disease without bulky mass [12,13]. Armitage suggested four R-CHOP cycles and, if complete remission is achieved, two more chemotherapy cycles or local radiation therapy can be delivered. In case of bulky disease, radiotherapy is mandatory after six R-CHOP cycles [8]. Same treatment was also proposed in the MINT study for localized bulky disease [11].

For localized disease with specific organ involvement, the therapeutic attitude is different. In case of primary DLBCL of the testis there is a significant risk of central nervous system (CNS) involvement, therefore R-CHOP associated to radiotherapy and Methotrexate or intrathecal (i.t.) Cytarabine is advised [14]. For patients displaying CNS involvement during their first presentation high dose i.v. and i.t. Methotrexate or Cytarabine-in case of lymphomatous meningitis-is recommended [15,16]. In case of altered cardiac function, R-CEOP can be advised [17].

Treatment of advanced stage DLBCL also witnessed several changes during the last 30 years. In the 80s, when IIIrd generation treatments, such as M-BACOD (Methotrexate, Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine and Dexamethasone), ProMACE/CytaBOM (Cyclophosphamide, Doxorubicin, Etoposid, Cytozar, Bleomycin, Vincristine, Methotrexate, Prednison) were developed, it was commonly believed that these regimens were more efficient than CHOP for advanced stage DLBCL patients [18,19]. Further studies comparing these regimens to CHOP on large number of patients proved no significant differences in complete remission or disease-free survival, but lower toxicity for CHOP [20].

GELA study analyzed R-ACVBP on 379 patients aged under 60 years, proving its superiority over the R-CHOP-21, but with higher toxicity. R-ACVBP includes Rituximab, Doxorubicin, Cyclophosphamide, Vindesine, Bleomycin, and Prednisone, for induction of remission, and consolidation with Methotrexate, Doxorubicin, and Cyclophosphamide [21].

For stage III-IV, low performance status, high serum LDH levels patients of younger age (<60 years), autologous stem cell transplantation can be advised as adjuvant therapy [8].

In case of relapsed and refractory DLBCL, prior to establishing salvage chemotherapy, a thorough patient assessment, with a personalized treatment based on age, co-morbidities and other patient-related factors being considered mandatory [22]. For late relapse, in patients with a good prognostic index, the initial regimen may be repeated [17]. In case of early relapse or refractory disease, several second line regimens may be followed in eligible patients by stem cell autotransplantation. None of the second line regimens, such as R-DHAP (Rituximab, Cisplatin, Cytarabine, Dexamethasone), R-ICE (Rituximab, Ifosfamide, Carboplatin, Etoposide), R-GDP (Rituximab, Gemcitabine, Dexamethasone, Cisplatin), ESHAP, BEAM (Carmustyne, Etoposid, Cytarabine, Melphalan) has been shown to be superior to the others [23]. However, a study carried out in 2014 by Crump et al. revealed that R-GDP (Rituximab, Cisplatin, Gemcitabine, Dexamethasone) has the same efficacy as R-DHAP but is less toxic [24].

A beacon of hope comes from the new therapies which are currently tested in non-Hodgkin lymphomas. Bortezomib, lenalidomide, mTOR inhibitors and new anti-CD20 monoclonal antibodies are recent therapies, which are being increasingly used in DLBCL treatment. Bortezomib is a proteasome inhibitor that inhibits NF-κB activity and in combination with chemotherapy has a better therapeutic response than single chemotherapy [25]. Lenalidomide is an analog of Thalidomide, an immunomodulatory and antiangiogenic agent that inhibits the secretion of proinflammatory cytokines. It demonstrated greater efficacy in the response rate for patients with non-germinal center DLBCL than those with lymphoma of the germinal center [26]. In a Phase 1 study, the efficacy of associating Ibrutinib, a new oral bruton tyrosine kinase inhibitor, together with R-CHOP was investigated, demonstrating good tolerability and possible improvement in response rate, but additional studies are needed to establish the exact role of this drug in DLBCL [27].

In hematological neoplasia, due to the graft-versus-host, the therapeutic potential of the immune system has been proven therefore its manipulation has become a very important treatment alternative. CARs (Chimeric antigen receptors) are artificial bio-constructs that recognize a tumor cell antigen and a molecule in the effector cell due to the T-activating domains

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of the composition, thus redirecting the T lymphocytes against neoplastic cells. T cells are collected from a patient by apheresis and then genetically modified to express CARs for redirection against the target neoplastic cells. Later they are multiplied in the laboratory, frozen and returned to the patient. They will recognize the neoplastic cells that have the target antigen on the surface and can remain in the body for a long time, resulting in complete lasting remissions. Results of clinical trials and distinct generations of CARs may result in a change in the therapeutic strategy in DLBCL [10,28].

Conclusions

Our study provided the scientific framework for the assessment of the efficacy of R-CHOP versus other Rituximab-associated regimens in patients with de novo DLBCL. The data indicated that there are no significant differences in treatment endpoints between the two groups, supporting the hypothesis that all three Rituximab-based regimens provide good therapeutic alternatives for DLBCL patients with dose-dependent adaptation based on age and comorbidities.

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Corresponding Author: Ş Patrascu, Department of Surgery, University of Medicine and Pharmacy of Craiova, Petru Rares St. No 2, Craiova, Romania, e-mail: stef.patrascu@gmail.com

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