

Efficacy of rituximab combined with CHOP for treating patients with diffuse large B-cell lymphoma

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ABSTRACT:

Background: The most persistent form of non-Hodgkin's lymphoma (NHL) is diffuse large B-cell lymphoma (DLBCL). It is the most common lymphoma, and 25% to 30% of individuals had localized disease upon presentation [1][2]. DLBCL exhibits a variety of clinical features in addition to perceptible heterogeneity in clinicopathology. DLBCL is largely treatable and chemosensitive. In individuals with DLBCL, the addition of anti-CD20 antibody to chemotherapy has significantly improved prognosis. The accepted standard of treatment for first-line DLBCL therapy is rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy. **Objective:** To determine if treating DLBCL with rituximab in addition to the CHOP regimen of chemotherapy is effective. **Conclusion:** In almost all the randomized trials comparing the combination with CHOP chemotherapy alone, adding rituximab to normal CHOP treatment significantly boosted complete remission rates, incident free survival, and overall survival.

I. INTRODUCTION:

The most persistent type of non-Hodgkin lymphoma (NHL) is diffuse large B-cell lymphoma (DLBCL). It is the most common lymphoma, and 25% to 30% of individuals had localized disease upon presentation [1][2]. DLBCL exhibits a variety of clinical features in addition to perceptible heterogeneity in clinicopathology. Regarding histomorphology, immunophenotype, biological behavior, and molecular genetics, it is similarly complex and multifaceted [3].

Despite belonging to a single class, DLBCLs are distinguished by extremely high levels of genotypic and phenotypic variability. Two primary DLBCL subgroups were identified by an initial genotypic and phenotypic differentiation based on gene expression profiling: activated B-

cell-like (ABC) and germinal-center B-cell-like (GCB) [4].

DLBCL is largely treatable and chemosensitive. The results for DLBCL patients have significantly improved when anti-CD20 antibodies are used along with to chemotherapy. The gold standard for first-line DLBCL therapy is now rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, which can improve long-term prognosis. Following six or eight rounds of first-line therapy, non-progressing patients enter what is known as the "watch and wait" period, during which time the disease is periodically staged until some improvement is noted. At that point, salvage therapy is initiated, despite the fact that it has a poor long-term survival rate. The majority of patients relapsed within the first 2 or 3 years. Now a recently developed pattern called maintenance therapy refers to the use of systemic therapy, either by continuing the primary drug or switching to a new one, in patients who get objective response or stable disease from the first-line chemotherapy [5][6].

Out of the patients responding to R-CHOP, 17%–40% may either advance or relapse after a partial remission (PR), and 12%–60% will become resistant to second- or third-line therapy, which may include autologous stem cell transplantation [7].

In 1997, the US Food and Drug Administration (FDA) authorized rituximab for the treatment of recurrent or refractory low-grade or follicular lymphoma (FL) NHL. The European Medicines Agency (EMA) then approved rituximab as MabThera (Roche, Basel, Switzerland) in 1998. Rituximab plus CHOP or another anthracycline-based chemotherapy was approved by the FDA in 2006 as the first-line treatment for DLBCL, following the evidence of improved efficacy outcomes linked to the combination treatment in clinical trials [8].

II. DISCUSSION:

The most prevalent subtype of non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), is a highly variable and severe illness [9]. With a slight male preponderance, incidence rises with age [10]. In order to identify DLBCL patients with the most aggressive illness, who can benefit from more rigorous therapy, researchers have concentrated their research efforts in the last few years on understanding the molecular features of these patients [11].

The varying clinical presentation, morphological, genetic, and molecular profiles of DLBCL emphasize the widespread belief that it is a complicated neoplastic illness. The identification of morphologic variations alone, such as immunoblastic DLBCL, has not been able to establish a reliable association with the clinical outcome, most likely due to the observers' subjective interpretations and experiences [12].

The standard treatment for cancer has been the cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) regimen, which was developed in the 1970s and is known for its exceptional response rate and minimal toxicity when compared to other regimens. The cure rate for DLBL has increased since rituximab (a monoclonal antibody against B-cell surface CD20 protein) was added to the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). As a result, it has been determined that this new regimen is the most successful thus far [13].

Rituximab:

An anti-CD20 monoclonal antibody called rituximab was given FDA approval in 1997. It is used in the management of autoimmune and lymphoproliferative diseases. Its purpose was to attach itself to the protein known as "CD20" found on the surface of B cells, which is an antigen. Upon attaching to CD20 positive cells, rituximab induces cell death by multiple pathways, such as complement-mediated cytotoxicity, antibody-dependent phagocytosis, and direct effects of rituximab binding to CD20. As of right now, the FDA has approved its usage in the following conditions: Pemphigus vulgaris, Microscopic Polyangiitis and Granulomatosis with Polyangiitis, Rheumatoid Arthritis, Chronic Lymphocytic Leukemia, and CD20 positive B-cell Non-Hodgkin's Lymphoma [15].

Since rituximab mainly targets B cells, it often has little adverse effects. "Infusion-related"

adverse effects are those that often occur within the first two hours of the initial infusion. Fever, chills, and shaking are among them; these can be treated by lowering the infusion rate or stopping the infusion altogether [16].

Diffuse large B-cell lymphoma:

The most common non-Hodgkin lymphoma globally is diffuse large B cell lymphoma (DLBCL), accounting for 30–40% of cases across various geographical locations. Usually, patients present with a rapidly expanding tumor mass in one or more nodal or extranodal locations. Most of patients arrive with a rapidly expanding tumor mass around one or more lymph nodes and extranodal locations. Extranodal illness affects about 40% of individuals at initial presentation. Virtually any tissue organ can be the primary site of DLBCL, but gastrointestinal tract is almost common site. About one-third of DLBCL patients have B symptoms, which include fever, weight loss, and sweats at night. Other individuals may have symptoms connected to organ dysfunction. Beta-2-microglobulin and serum lactate dehydrogenase (LDH) are frequently elevated above normal [17].

Mature B-cells at various stages of differentiation give rise to DLBCL. Different gene mutations induce alterations in B-cells that lead to altered gene expression and the development of neoplastic transformations. After releasing from the bone marrow, B lymphocytes go to secondary lymphoid tissues during ontogeny, where they will encounter specific antigens that stimulate the growth of secondary follicles. At this location, B-cell development enters an antigen-dependent phase. These lymphocytes are transformed into highly proliferating centroblasts in the germinal center of the secondary follicle, where frequent and persistent somatic mutations of the immunoglobulin variable chain genes occur, encouraging maturation and differentiation into centrocytes, which in turn become plasma cells or memory B-cells. BCL2 gene expression is often downregulated and BCL6 gene expression is hyperexpressed in the germinal center [18].

A surgical specimen/excisional lymph node, or extranodal tissue biopsy that provides sufficient material for formalin-fixed samples should be used to make the diagnosis. When a core biopsy is the only diagnostic procedure necessary for a rare patient in need of immediate care, it may be relevant. Only the bare minimum of CD45, CD20, and CD3 immunohistochemistry is

necessary. While gene expression profiling is still under investigation, it is advised to collect fresh frozen material for molecular analysis. It is necessary to guarantee processing by an experienced pathology institute in order to assure adequate quality. The diagnosis should be provided by the histology report in accordance with the most recent WHO classification [19].

The NHL, including DLBCL, uses the Ann Arbor staging method the most frequently. This approach was chosen for use in NHL after it was first described in 1971 for staging Hodgkin disease based on the contiguous nodal spread of that illness [20].

Stages	Location of disease
Stage I	Involvement of a single lymphatic region(I) or localized involment of single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymphatic regions on the same side of the diaphragm(II) or localized involment of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm(IIF)
Stage III	Involvement of lymphatic regions on both side of the diaphragm
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement

Table: Staging of lymphoma

The therapy of DLBCL is often approached through two distinct treatment algorithms: one for localized disease (Ann Arbor stages I and II) and another for advanced disease (stages III and IV). With a long-term overall survival (OS) rate of about, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (CHOP) chemotherapy delivered every 21 days (CHOP21) remained the mainstay treatment for DLBCL until recently. Eventually, a number of studies looked on changing the dose-intensity and dose-density of the CHOP regimen in an effort to increase its effectiveness. In 1997, rituximab is the first monoclonal antibody approved for use by the Food and Drug Administration for follicular lymphoma, and this immunotherapy was soon applied to DLBCL and other B-cell NHLs. In DLBCL, rituximab considerably enhances the effectiveness of treatment. Using rituximab combined with CHOP (R-CHOP) therapy, patients with DLBCL had better overall survival (OS) according to a major randomized phase III research [21].

The final results of the non-interventional research MabScale were studied by Jan Dürig et al. in patients with follicular lymphoma and diffuse large B cell lymphoma using subcutaneous rituximab. Subcutaneous (SC) rituximab's safety and efficacy in standard clinical practice were the subjects of this investigation. It was found from the study that rituximab SC was safe and effective in treating both DLBCL patients and follicular lymphoma patients [22].

Role of rituximab in first-line therapy of high-risk diffuse large B-cell lymphoma: a retrospective review by the Polish Lymphoma Research Group was studied by Wojciech Jurczak et al. The trial aims to examine the potential benefits of rituximab in addition to anthracycline-based chemotherapy for patients with DLBCL who are classified as high-risk by the IPI. Among them were 371 high-risk DLBCL patients who were receiving care at 15 hematological institutes in Poland. Based on the overall response and progression free survival, the researchers deduced from the trial that adding rituximab to CHOP treatment greatly enhances the prognosis of patients with high-risk DLBCL [23].

A cost-utility and budget impact analysis were carried out by Septiara Putri et al. in their study, "Adding rituximab to chemotherapy for diffuse large B-cell lymphoma patients in Indonesia." Despite the study's suggestion that rituximab was rather pricey, it still seemed to be a good investment because R-CHOP had a major positive impact on health [24].

Rituximab is used to treat diffuse large B cell lymphomas, according to Gerhard Held et al. In every randomized trial comparing the combination with CHOP chemotherapy alone, the addition of rituximab to normal CHOP treatment resulted in a significant increase in complete remission rates, incident free survival, and overall survival [25]. In Malawi, Stephen Kimani et al. conducted a prospective, single-arm, non-randomised phase 1/2 clinical trial to examine the

safety and effectiveness of rituximab in patients with diffuse large B-cell lymphoma. They concluded from the study that R-CHOP would be practical, secure, and beneficial for DLBCL patients in Malawi [26].

III. CONCLUSION:

In summary, there is a great deal of ongoing variability in DLBCLs (as well as lymphomas generally) in terms of clinical, morphological, and molecular diagnostic features. In nearly all of the trials that compared the combination with CHOP chemotherapy alone, adding rituximab to normal CHOP treatment has significantly boosted complete remission rates, event-free survival statistics, and overall survival. Despite the comparatively high cost of the medication, R-CHOP continues to offer great value for money due to its substantial health advantages. Finally, R-CHOP therapy may be practical, secure, and beneficial for DLBCL patients.

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List of Abbreviation and Full form

Abbreviation	Full form
DLBCL	Diffuse large B-cell lymphoma
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
NHL	Non-Hodgkin lymphoma
IPI	International prognostic index
ABC	Activated B-cell
GCB	Germinal-center B-cell
R-CHOP	Rituximab, Cyclophosphamide, doxorubicin, vincristine, and prednisone