

DIFFUSE LARGE B-CELL LYMPHOMA

Union for International Cancer Control

2014 Review of Cancer Medicines on the WHO List of Essential Medicines

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Executive Summary

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), constituting up to 40% of all cases globally.[1] This subtype of cancer is heterogeneous and aggressive, yet scientific advances in the last quarter century have rendered it curable with chemotherapy or with combined chemotherapy and immunotherapy. Until 1998, the standard regimen for DLBCL treatment included cyclophosphamide, vincristine, doxorubicin, and prednisone, referred to as “CHOP.” The standard of care in the United States, Europe, and other high-income settings now includes a combination of the four chemotherapy drugs plus immunotherapy with the humanized monoclonal antibody directed at CD20, rituximab (R-CHOP). Research demonstrates 55.8% survival at 6 years among patients receiving CHOP only, and 74.3% among patients on R-CHOP. [2] The chance of survival without chemotherapy is 0%. Thus, with the addition of CHOP alone, gains in survival go from 0% to 56%. Drugs comprising CHOP are all old, off-patent drugs, while rituximab remains on patent, is more costly, and technically more difficult to administer. Adding rituximab to CHOP results in an increase in long-term survival of almost 20%. We are recommending that rituximab be added to the Essential Medicines List and that R-CHOP be viewed as the standard regimen for this disease. In settings where rituximab is not available, CHOP should still be utilized since many patients will benefit from its use.

Public Health Relevance

Decades of surveillance on the burden of DLBCL in the United States, Europe, and several other high-income settings have shed light on the burden of disease. For example, according to the United States National Cancer Institute’s SEER Database, incidence is approximately 7 per 100,000, affecting to a greater extent adults over 60 years, though it occurs in patients of all ages, including children. Although global epidemiological data on DLBCL burden are limited, the combined knowledge generated from discrete studies and international estimates of the overall burden of NHL (e.g. GLOBOCAN 2008 and 2012) warrants urgent action to expand access to chemotherapy drugs and where possible, immunotherapy.

According to the International Agency for Research on Cancer (IARC), the age standardized incidence rate of non-Hodgkin lymphoma among both sexes worldwide is estimated at 5.0 per 100,000 people. Data from the GLOBOCAN 2012 report shows an age standardized rate in more developed regions being more than double that in less developed regions (8.6 and 3.6, respectively). However, it is plausible that this difference reflects lagging detection and diagnostic capacity in poorer parts of the world. A similar scenario was observed in United States in the late 20th century: improvements in detection methods in the 1980s are considered to be one of the causes of significant increase in incidence during this timeframe, followed by a

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plateau ever since.[3] A growing epidemic of human immunodeficiency virus (HIV) in the United States at that time is understood to have contributed to the increased incidence as well.[4] The mortality rate differential between more and less developed regions of the world is less pronounced than that of incidence (2.7 and 2.3 per 100,000 respectively).[5]

Research on DLBCL in particular offers further insight into the impact of this disease in under-resourced parts of the world. A recent study by Laurini and colleagues reported on the burden of NHL subtypes in Central and South America analyzing 1028 consecutive cases drawn from four academic medical centers and one private laboratory. This research demonstrated that DLBCL comprised 40.0% of all forms of NHL, a higher proportion than that recorded in the United States and Europe.[6] A retrospective adult cohort analysis in Mashhad, Iran analyzing data on 391 patients also showed that DLBCL was the most common subtype of NHL.[7] These studies, coupled with epidemiological data from the aforementioned international database GLOBOCAN, support the conclusions that the burden of DLBCL is not confined to high-income settings, and that treatment options must be made available internationally.

Requirements for diagnosis, treatment, and monitoring

Diagnostics: Pathologic analysis of surgically excised lymph node or extranodal tissue is required. If treatment with R-CHOP is possible, basic immunohistochemistry is required to detect the presence of the antigen CD20, located on the surface of the malignant B-lymphocytes, which rituximab targets. A minimum diagnostic panel (where possible) should also include LDH (for IPI determination), as well as immunohistochemistry CD20. When available, an enhanced diagnostic panel might include CD10, BCL6, MUM-1 to subtype DLBCL between germinal center and ABC subtypes.

Testing: It has been recommended that pre-treatment tests include staging utilizing contrast-enhanced computed tomography (CT) scan, and blood counts and chemistries to assess critical organ function, including renal and hepatic function. The role of pre-treatment cardiac assessment with echocardiography is uncertain, but many feel is not required.[8] Status of hepatitis B and C should be assessed, and monitored closely if positive.

Administration and Care of Patients: Administration requires intravenous infusion capacity, and requires that the patient have regular access to clinical care. In developed countries administration is usually performed in out-patient facilities, though in other setting, patients may be treated in in-patient facilities. IV hydration and anti-emetics should accompany administration of both CHOP and R-CHOP. Doxorubicin and vincristine require care monitoring to prevent soft tissue extravasation which can cause severe local reactions and necrosis. Rituximab can cause severe allergic reactions and must be given slowly, with close monitoring supportive medicines readily available. If the patient has evidence of hepatitis B or C infection, this should be monitored since administration of rituximab can re-activate either of these infections with severe consequences.

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Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself, including bone marrow suppression, infection, allergic reactions to rituximab, and gastrointestinal toxicity.

Social and financial wellbeing can be impacted by treatment side effects and should be monitored and addressed as well.

Overview of Regimens

The following tables include basic information on administration and dosing for CHOP and R-CHOP, and exclude ancillary medications pertaining to the management of side effects. For either therapeutic regimen (CHOP or R-CHOP) 6 cycles of therapy is recommended.

Standard Regimen

R-CHOP: Chemotherapy plus monoclonal antibody, 6 cycles

<i>Rituximab</i>	Intravenous infusion	375 mg/m ²
<i>Cyclophosphamide</i>	Intravenous infusion	750 mg/m ²
<i>Doxorubicin</i>	Intravenous injection	50 mg/m ²
<i>Vincristine</i>	Intravenous infusion	1.4 mg/m ² (cap dose at 2 mg)
<i>Prednisone</i>	PO (oral liquid or tablet)	100 mg

Note: in the case where rituximab is not available, CHOP should be utilized since many patients will benefit from this regimen.

Alternative Regimens recommended by some consultants, but not considered primary recommendations: R-ACVBP (rituximab, cyclophosphamide, doxorubicin, vindesine, bleomycine and prednisolone) showed overall survival advantage over R-CHOP in a prospective randomized study (Recher C et al. Lancet 2011). Most consultants felt that R-CHOP and CHOP remained standard of care, and that this randomized trial might have been flawed, and R-ACVBP was not widely accepted, and vindesine often not available.

Review of Benefits and Harms

Benefits

Given that patients diagnosed with DLBCL who do not receive treatment cannot survive, the benefits of the Essential Regimen of CHOP are highly significant. In the GELA LNH-98.5 study, previously untreated patients (60-80 years old) had improved overall survival and progression-free survival on both chemotherapy and chemotherapy plus Rituximab; the addition of Rituximab to the regimen was found to significantly improve outcomes.[9] A similar study among younger adult patients (18-60 years) produced similar results, with 59% event-free survival at 3 years among patients on CHOP-like chemotherapy, and 79% EFS among patients on CHOP-like chemotherapy and Rituximab.[10] A systematic review by Cheung and colleagues

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compiled these studies and others to compare outcomes among patients on chemotherapy versus those on chemotherapy plus Rituximab (R-CHOP) for the treatment of lymphoma. As a subset of the larger review, 11 randomized controlled trials concerning the treatment of aggressive histology non-Hodgkin lymphoma (DLBCL) were analyzed. This review, among others, have demonstrated the clinically important benefits to overall and progression-free survival among patients on chemotherapy with rituximab or those on chemotherapy alone.[9, 11-21] It is important to note that those patients who remain in remission at 5 years are likely cured of their disease and have a high probability of leading normal lives. Since many patients are young this results in many life-years gained.

CHOP or R-CHOP can be given every 21 days without hematopoietic growth factor support. Both regimens can also be given every 14 days with white cell growth factor (G-CSF) support, but the benefit from the every 14 day regimen is not clear, and the additional cost of G-CSF support is substantial.

Harms and Toxicity Considerations

Common

Patients receiving CHOP and R-CHOP will experience alopecia, and blood count suppression, particularly neutropenia, which increases the risk of infection. The incidence of grade 3 or 4 infection in these patients is 7-20%. [9,10,12] Neuropathy from vincristine is rare and usually mild and reversible.

Rituximab can cause significant systemic allergic reactions during administration, special precautions must be taken particularly during the first infusion. It is important that rituximab is administered slowly and that medicines are available both as premedications and to treat allergic reactions as required. Rituximab may also cause neutropenia and, infrequently, viral infection or reactivation of latent viral infection, including viral hepatitis.

Serious

Doxorubicin is associated with a risk of congestive heart failure. This risk is dose-dependent and at the doses delivered with 6 cycles of CHOP or R-CHOP (300 mg/m²), the risk is small, and far out-weighed by potential benefits of treatment. The risk of long-term bone marrow damage, including secondary malignancies such as myelodysplastic syndrome or acute myeloid leukemia is very small (less than 1%). The risk of other second malignancies with CHOP and R-CHOP is also small.[10]

Systematic Reviews

Ruiz-Delgado, G. J., *et al.* Is there a benefit to adding rituximab to CHOP in the overall survival of patients with B-cell non-Hodgkin's lymphoma in a developing country? *Hematology*. **17**(4), 193-197 (2012).

Abstract: Rituximab (R) has changed the prognosis of patients with non-Hodgkin's lymphoma (NHL) in developed countries, but its role has not been analyzed in

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underprivileged circumstances. One hundred and two patients with NHL treated in a developing country were analyzed: 28 patients with follicular lymphoma (FL) and 74 with diffuse large B-cell lymphoma (DLBCL). Patients were treated upfront with either cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or R-CHOP; the decision to employ R depending solely on the ability of patients to defray it. In DLCL, 42 were given CHOP and 32 R-CHOP, whereas in FL, 19 were given CHOP and 9 R-CHOP. The impact of the addition of R was found to be clearer in FL than in DLCL. In patients with DLCL, the overall survival (OS) was 87% at 80 months for those treated with R-CHOP and 84% at 145 months for those treated with CHOP (not significant). In patients with FL, the OS was 89% at 88 months for those treated with R-CHOP and 71% at 92 months for those treated with CHOP ($P = 0.05$). In a multivariate analysis, other variables which were identified to be associated with the OS were IPI and number of cycles in DLCL. It is concluded that R produced a mild positive impact in the OS of patients with FL, but not in those with DLCL. Since the addition of R results in a 36-fold increase in treatment costs, these observations may be important to decide therapeutic approaches in NHL patients living in underprivileged circumstances.

Hiddemann W, et al. Front-line therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) significantly improves the outcome of patients with advanced stage follicular lymphomas as compared to CHOP alone—results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). *Blood*. 106: 3725–32 (2005).

Abstract: Phase 2 studies suggest that the monoclonal antibody rituximab may improve the prognosis of patients with follicular lymphoma (FL) when it is added to chemotherapy. In the current study, 428 patients with untreated, advanced-stage FL were randomly assigned for therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) alone ($n = 205$) or CHOP combined with rituximab (R-CHOP) ($n = 223$). R-CHOP reduced the relative risk for treatment failure by 60% and significantly prolonged the time to treatment failure ($P < .001$). In addition, a significantly higher overall response rate (96% vs 90%; $P = .011$) and a prolonged duration of remission ($P = .001$) were achieved. In spite of a relatively short observation time, these beneficial effects even translated to superior overall survival ($P = .016$), with 6 deaths in the R-CHOP group compared with 17 deaths in the CHOP group within the first 3 years. The predominant treatment-related adverse effect was myelosuppression. Severe granulocytopenia was more frequently observed after R-CHOP (63% vs 53%; $P = .01$). However, severe infections were rare and of similar frequency after R-CHOP and CHOP (5% and 7%). Hence, adding rituximab to CHOP significantly improves the outcome for patients with previously untreated advanced-stage FL and does not induce major adverse effects.

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Additional reviews and analyses summarize the literature supporting the use of CHOP and R-CHOP for the treatment of DLBCL.

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- Cunningham, D., *et al.* Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *The Lancet*. **381**(9880), 1817-1826 (2013).
- Shankland, K. R., Armitage, J. O., & Hancock, B. W. Non-Hodgkin lymphoma. *The Lancet*, **380**(9844), 848-857 (2012).

Recommendations

The reviewers recommend the incorporation of DLBCL treatment options into the WHO Model List of Essential Medicines, and recommend specifically that rituximab be added to the core Essential Medicines List.

Additions proposed for Section 8.2 of the EML

Rituximab

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