

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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R2-CHOP vs R-CHOP for Diffuse Large B-Cell Lymphoma



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H&O How did rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) become the standard of care for the treatment of diffuse large B-cell lymphoma (DLBCL)?

NF For many years, CHOP chemotherapy was the standard treatment for DLBCL. Although efforts to improve outcomes with CHOP had been ongoing for years, the addition of rituximab was the first—and so far it is the only—agent to show a clinical benefit. Randomized trials demonstrated that adding rituximab to CHOP led to improvements in both progression-free survival and overall survival. As a result, R-CHOP is now considered the standard of care for newly diagnosed patients in most settings.

H&O Does R-CHOP work equally well for all subtypes of DLBCL?

NF No. Studies have shown that patients with the activated B-cell (ABC) subtype of DLBCL experience inferior outcomes with R-CHOP compared with patients with other subtypes.

H&O What does R2-CHOP refer to?

NF *R2-CHOP* refers to the addition of lenalidomide (Revlimid, Celgene; the *R* is for Revlimid) to the R-CHOP regimen. Since the advent of R-CHOP, no randomized studies have found any improvements to this approach. However, Dr Grzegorz Nowakowski reported

intriguing findings at the 2014 annual meeting of the American Society of Clinical Oncology (ASCO) from a phase 2 study of R-CHOP plus lenalidomide, a regimen now referred to as R2-CHOP.

H&O Why do patients with ABC-DLBCL not respond as well to R-CHOP as other patients?

NF It is unclear why these patients tend to fare worse. We know that pro-survival signaling cascades, including the nuclear factor κ B (NF κ B) pathway, are activated in ABC DLBCL, and this pathway may give these cells a survival advantage in comparison with germinal center (GC) lymphoma. There are some preclinical data suggesting that lenalidomide interferes with the NF κ B pathway or signaling within that pathway. This agent does not directly affect NF κ B but appears to target some of the kinases that are likely turned on in this pathway. This biological difference could explain why the addition of lenalidomide to R-CHOP appeared to improve outcomes among patients with the ABC subtype but not among those with the GC subtype.

A subset analysis from a phase 2 study of single-agent lenalidomide in relapsed DLBCL also suggested that patients with the ABC subtype experienced a greater benefit than patients with the GC subtype (This study was published in the *Annals of Oncology* with Witzig as the first author). Data from this study and early preclinical studies provided the rationale for adding lenalidomide to R-CHOP for untreated patients.

H&O What did this phase 2 study demonstrate about R2-CHOP for DLBCL?

NF In this nonrandomized phase 2 study, patients who had the ABC subtype of DLBCL experienced outcomes similar to those of patients who had the germinal center (GC) subtype. The addition of lenalidomide appeared to improve outcomes for patients with the ABC subtype compared with what this group of patients usually experiences with R-CHOP treatment.

H&O Could you discuss the findings of the phase 2 study presented at the ASCO annual meeting earlier this year?

NF A total of 55 patients were evaluable for response, 33 with GC DLBCL and 22 with non-GC DLBCL. The 2-year progression-free survival for patients treated with R2-CHOP was 60% (n=20) among patients with the GC subtype and 50% (n=11) among patients with the non-GC subtype. The 2-year overall survival rates were 83% and 75%, respectively.

The similarity in the outcomes of these 2 arms is striking. With other treatment regimens, the difference between these 2 groups has been much wider. For example, the study authors conducted a case-matched historical analysis showing 2-year progression-free survival rates of 64% for GC patients vs 28% for non-GC patients following R-CHOP therapy.

H&O Were outcomes also improved for patients with the GC subtype?

NF For this group of patients, the overall response rate was similar to what has been observed with R-CHOP.

H&O Were there any side effects of concern?

NF The authors did note some cytopenias and neutropenia, which was the most common serious toxicity. Some patients also experienced thrombocytopenia and anemia. However, these side effects were manageable. Neutropenic fevers were rare.

H&O Following the presentation of this study, have you considered treating patients with the ABC subtype with R2-CHOP?

NF Additional data are needed before a practice change is warranted. But patients with the ABC subtype typically have a poor prognosis. It was very encouraging to hear the results of this study.

H&O Should R2-CHOP be considered as frontline therapy for DLBCL?

NF It is not possible to draw that conclusion from this small, phase 2 study. Additional work is needed in order to understand the benefit of R2-CHOP for this disease. Fortunately, there is an ongoing phase 3 trial comparing R-CHOP with R2-CHOP; the phase 2 study described here provides the rationale. The phase 3 study will enroll only patients with the ABC subtype.

H&O What do the outcomes of this phase 2 study indicate about the biology of DLBCL?

NF The results of this study confirm that there are biological differences between the 2 subsets of patients. In addition, they confirm that a targeted agent can exploit these differences in order to improve outcomes.

The mechanism of action of lenalidomide is still a matter of some debate. But clearly this agent is not traditional genotoxic chemotherapy, and is not indiscriminately killing all dividing cells. Rather, it affects the biology of the cell. It targets specific pathways. If there were no real biological difference between the 2 subtypes of patients, then R-CHOP would have the same benefit for all patients.

Lenalidomide also has been shown to increase antibody-dependent cellular cytotoxicity (ADCC). So this drug may have 2 mechanisms of action in the treatment of lymphoma: by attacking the pathways described above and also by increased ADCC. Lenalidomide modulates, and may trigger, antitumor immune responses in the microenvironment in certain types of lymphomas. It may be that adding this agent to rituximab has a synergistic effect because lenalidomide activates the immune system.

H&O Do you envision eventually eliminating CHOP from the treatment regimen entirely?

NF It would be ideal to eliminate chemotherapy in the frontline treatment of DLBCL. With other types of lymphoma, treatment is already moving in that direction. For example, there is a large, ongoing, randomized phase 3 study of indolent lymphoma in which CHOP is being eliminated from the regimen for one group of patients. However, we do not yet have enough data to eliminate chemotherapy from the treatment regimen for aggressive lymphomas, especially because many patients are curable.

In drug development, researchers often try to introduce biologic agents into the relapsed setting and, if the response rates are high enough, then the frontline setting. Or, if response rates are high enough, then one can consider using biologic agents only—without che-

motherapy—for patients who may have a difficult time tolerating harsher medications.

H&O Are there any other biologic agents that you would want to see added to R2-CHOP to further improve outcomes?

NF Absolutely. Ibrutinib is a very interesting compound that has demonstrated a benefit for patients with mantle cell lymphoma and chronic lymphocytic leukemia. There are preclinical data showing that ibrutinib has activity in ABC DLBCL. I hope to see a study of ibrutinib added to the combination of lenalidomide, rituximab, and CHOP.

Other biologic agents also may have activity in DLBCL. For example, ABT-199, which is a BCL-2 inhibitor, could be combined with R2-CHOP or R-CHOP, as could several phosphatidylinositol 3-kinase (PI3K) inhibitors currently in development.

H&O The phase 3 trial of R2-CHOP that is ongoing will likely take years. Having seen the phase 2 results, is it difficult to wait for confirmation from a large, randomized study?

NF Especially in a population where there is already a potential to cure patients in the frontline setting, it is important to await solid phase 3 data, not only for efficacy but also for toxicity. Lenalidomide does have side effects, and there is always a risk of long-term toxicity. We need longer follow-up on the phase 2 study and we need phase 3 data before we can add lenalidomide to R-CHOP as part of our routine clinical practice.

Suggested Reading

Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. *Cancer*. 2011;117(22):5058-5066.

Nowakowski GS, LaPlant B, Macon WR, et al. Effect of lenalidomide combined with R-CHOP (R2CHOP) on negative prognostic impact of nongerminal center phenotype in newly diagnosed diffuse large B-cell lymphoma: a phase 2 study [ASCO abstract 8520]. *J Clin Oncol*. 2014;32(5)(suppl).

Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. *Leukemia*. 2013;27(9):1902-1909.

Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. *Ann Oncol*. 2011;22(7):1622-1627.

(continued from page 607)

identified: a genomic deletion of 27 base pairs in codons 400 to 408, located at the boundary of the cytoplasmic and first transmembrane domain of band 3. Thus, hereditary ovalocytosis is unique among red cell membrane disorders in that the identical mutation in a single gene is responsible for the morphologic phenotype.

Regarding hereditary stomatocytosis, both the dehydrated and overhydrated forms exhibit a cation leak to the univalent cations Na⁺ and K⁺ that results in altered intracellular cation content and cell volume alterations. Several recent studies, including one by Dr Ryan Zarychanski and colleagues at the University of Manitoba, have shown that dehydrated hereditary stomatocytosis is associated with mutations in PIEZO1. However, the molecular basis for overhydrated hereditary stomatocytosis has not yet been defined.

Suggested Readings

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Zarychanski R, Schulz VP, Houston BL, et al. Mutations in the mechanotransduction protein PIEZO1 are associated with hereditary xerocytosis. *Blood*. 2012;120(9):1908-1915.