Editorial Commentary

Indolent non-Hodgkin lymphoma treatment in the new drugs era

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Sufficient scientific evidence supports the use of immunochemotherapy regimens with anti-CD20 Rituximab. Rituximab is included in most initial and subsequent therapy for patients with mantle cell lymphoma (MCL) and indolent non-Hokdgin's lymphoma (NHL).

In 2005, two different groups published promising results regarding the use of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), showing an improvement in progression free survival (PFS) (1), and the combination of rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) with an improve in the overall survival (OS) (2).

A few years later, Bendamustine (an alkylating agent) demonstrated clinical activity in patients with indolent NHL that progressed within 6 months of treatment with any therapy with rituximab (3).

In 2014, Flinn *et al.*, published the results of the BRIGHT clinical trial, which was designed to compare the safety and efficacy of bendamustine and rituximab (BR) compared with standard of care therapies (R-CHOP and R-CVP) in patients with newly diagnosed indolent HNL or MCL requiring treatment. After analyzing 447 patients the BR regimen was found to be noninferior to standard therapy in terms of CR rates. The overall response rates were higher for the BR treatment group compared with the standard-therapy. The difference in CR rates between the two groups were greatest in patients treated with R-CVP, although this was not statistically significant (4).

In April of this year, the results of the 5-year follow up of the BRIGHT study was published. The median follow-up was now 65.0 months for both groups (R-CHOP/R-CVP and BR). In the final paper the results for the secondary endpoints of PFS, event-free survival (EFS), duration of response (DOR), and OS were presented but, information about adverse events (AEs) were not collected during this period of extended follow up (5).

Analysis of the endpoints were in favor of the BR group in terms of PFS, EFS and DOR when comparted to R-CHOP/R-CVP. The best results were seen in the MCL subgroup. However, no evidence was presented to show that OS was improved in the BR group. This may be due to the fact that the BR regimen was given in some patients who previously received R-CHOP/R-CVP. An important observation was, that the maintenance treatment with Rituximab did not contribute to creating differences in the results. The updated BRIGT study data were consistent with those seen in the StiL NHL1 study which favored BR in terms of a prolongation of time to next treatment but showed no difference in OS between the two study groups (6). The safety profile, of both treatment groups, was similar with no substantial difference in early non-disease mortality.

The safety profiles of BR, R-CHOP, and R-CVP were as expected. In the paper published in 2014, it was demonstrated that BR has a unique safety profile distinct from that of the standard chemotherapy regimens. Both regimens have presented Hepatitis B reactivation cases, as published by previous studies (7). Screening HBV is recommended in patients receiving anti-CD20 antibodies,

and in patients found to be seropositive for HBV should be treated prophylactically for 6–12 months after cessation of the therapy. Entecavir and tenofovir as first-line antiviral have demonstrated greater efficacy for the prevention and treatment of this virus reactivation (8).

The major limitations with impact PFS in these studies were the open-label design and the lack of prespecified imaging follow-up. The data was conclusive that the BR regimen provides better disease control than R-CHOP/R-CVP, with fewer patients requiring second-line treatment. The lack of improvement in OS in patients receiving BR compared to R-CHOP/R-CVP suggests that all regimens remain an option in these patients.

But, in the era of the new agents like Ibrutinib (Bruton tyrosine kinase inhibitors), Venetoclax (BCL-2 inhibitor), and Obinutuzumab (type II anti CD20), this landscape may change. Some studies have published the results of the association of Bendamustine with new agents in the treatment of indolent NHL, with important results. Studies such as GADOLIN, a phase III trial, which showed greater efficacy of the association Bendamustine plus Obinutuzumab followed by maintenance with Obinutuzumab *vs.* Bendamustine monotherapy, in refractory to rituximab FL patients (9).

We are sure that the information coming from studies underway will help us better understand the role of BR in the future for indolent lymphomas *vs.* novel agents, nevertheless, the combination of these new drugs to conventional chemotherapeutic treatments represent a better scenario than some years ago.

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References

1. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-32.
2. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417-23.
3. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. Cancer 2010;116:106-14.
4. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-52.
5. Flinn IW, van der Jagt R, Kahl B, et al. First-Line Treatment of Patients With Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma With Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. J Clin Oncol 2019;37:984-91.
6. Rummel M, Maschmeyer G, Ganser A, et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (R-CHOP) as first-line treatment in patients with indolent lymphomas: Nine-year updated results from the Stil NHL1 study. J Clin Oncol 2017;35:abstr 7501.
7. Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 2009;27:605-11.

8. Kelling M, Sokol L, Dalia S. Hepatitis B Reactivation in the Treatment of Non-Hodgkin Lymphoma. Cancer Control 2018;25:1073274818767879.
9. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2016;17:1081-93.

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