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New Insight for the Treatment of Follicular Lymphoma in Relapse: The Role of Obinutuzumab

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Abstract

In patients who relapse early in the course of treatment, patients with low grade lymphoma need new standards since most patients become resistant to subsequent treatment. A number of novel therapies are being examined in this setting, including monoclonal antibodies, immunoconjugates, immunomodulatory agents, and signal transduction inhibitors. Recently, with data accumulation treatment options moved from CHOP (cyclophosphamide–doxorubicin–vincristine–prednisone) to rituximab and chop or rituximab and cvp (cyclophosphamide–vincristine–prednisone) and from R-CHOP to bendamustine and rituximab, so treatment decisions in the relapsed and refractory setting have become more complex. The choice of subsequent treatment must consider type of upfront treatment; duration of remission; and patient-related factors such as age, comorbidities, and treatment preferences. This paper summarizes the evidence for novel therapies especially the emerging role of type II anti CD20.

Keywords: Lymphoma; Antibodies; Obinutuzumab

Introduction

Non-Hodgkin lymphoma (NHLl) is the most common hematologic malignancy in North American adults, accounting for 4.5% of all new cancer cases in men and 3.8% in women in 2015 [1]. Rates continue to rise with age, with the reported incidence having increased 0.3% per year in men and 0.4% per year in women between 2001 and 2010. Of the indolent NHLs, follicular lymphoma (FL) is the most common subtype, constituting up to 22% of all cases in with an incidence of more than 1500 cases annually [2]. Although approximately 20% of patients will not require therapy for the first 10 years after diagnosis, most will experience progressive disease needing treatment [3]. Until recently, the standard initial treatment for FL was Rituximab with either cyclophosphamide–doxorubicin–vincristine–prednisone (R-chop) or cyclophosphamide–vincristine– prednisone (R-cvp). However, data from the stil-1 study by Rummel *et al.* in 2013 reported a significantly higher response rate and longer progression-free survival (PFS) with Bendamustine–Rituximab (BR) than with R-chop (PFS: 69.5 months vs. 31.2 months; $p < 0.0001$) after a median follow-up of 45 months [4]. In addition, (BR) was clearly associated with an improved safety profile. Updated results presented at the American Society of Hematology 2014 annual meeting showed that median time to next treatment in the BR group still had not been reached after a median follow-up of 87 months [5]. In the stil-1 trial, maintenance Rituximab was not given, but maintenance is routinely used; therefore, time to next treatment could in reality be even longer with BR.

Follicular Lymphoma: Disease in Relapse

In recurrent (FL), the goal of therapy is to improve disease-free survival with maintaining a good quality of life. Most studies in the relapsed setting have included patients who received Rituximab-based chemotherapy other than BR as induction, complicating the subsequent choice of treatment. However, duration of remission is an important factor in treatment decisions. Data from the National Lympho Care Study in the United States demonstrated that patients receiving R-chop in the first line whose disease progressed within 2 years after diagnosis experienced lesser 5-year overall survival (OS) than did those whose disease did not progress within 2 years (50% vs. 90%)8. Therefore, where relapse occurs more than 2–3 years after upfront treatment, it might be reasonable to use the same approach for subsequent treatment. However, where relapse occurs early, such as before 6 months, a novel approach is needed. In practice, treatment strategies vary and include re-challenge with the initial treatment regimen, use of a non-cross-resistant treatment regimen with or without Rituximab, high-dose chemotherapy with autologous or allogeneic stem-cell transplantation (SCT), or when possible, consideration of an appropriate clinical trial [6].

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In the stil-1 study, subsequent treatments for patients randomized to receive BR in the first line included repeated treatment with (BR) (22%) or treatment with R-chop (31%) or a Fludarabine-based regimen (10%)5. In addition, the stil-2 study compared treatment with BR or Fludarabine–Rituximab in the relapsed setting, in which 11% of patients receiving (BR) had previously received the same regimen as at induction [7]. After a median follow-up of 96 months, the overall response rates (ORRs) in the (BR) and Fludarabine–Rituximab groups were 82% and 51% respectively, and the associated median PFS durations were 34.2 months and 11.7 months ($p < 0.0001$). In addition, compared with patients receiving Fludarabine–Rituximab, those receiving (BR) experienced a longer median overall survival (OS) (109.7 months vs. 49.1 months, $p = 0.012$). However, a subgroup analysis of data for patients receiving upfront (BR) was not reported; it is therefore unclear whether the response in those patients was as good as it was in the patients who were Bendamustine-naïve.

Monoclonal Antibodies

In FL, Rituximab has revolutionized treatment, and it is recommended for use in combination with chemotherapy, followed by maintenance monotherapy [2]. However, not all patients respond to Rituximab-containing regimens in the first line, as evidenced by data from stil-1, in which about 8% of patients did not achieve a response to their randomized treatment [4]. Furthermore, a number of additional patients will relapse or progress during their 2 years of maintenance therapy, as was seen in the prima study of maintenance Rituximab after first-line treatment with either R-chop, R-cvp, or Rituximab with Fludarabine–cyclophosphamide–mitoxantrone [8,9].

Obinutuzumab

Obinutuzumab is a type II anti-CD20 mAb that was designed to improve on the therapeutic activity of Rituximab [10]. In addition it induces nonapoptotic direct cell death, with less complement activation. In preclinical studies, Obinutuzumab demonstrated superior activity over Rituximab, with increased direct cell death, antibody-dependent cell-mediated cytotoxicity, and B-cell depletion in whole human blood and lymphoid tissues from non-human primates [10]. Among all the novel mAbs, Obinutuzumab is the furthest into development, with data available from a total of four studies examining its use either as monotherapy or in combination with chemotherapy [11,12].

The phase II Gauss study compared Obinutuzumab with Rituximab monotherapy in patients with relapsed and refractory FL not refractory to Rituximab [10]. A numerically superior ORR of 45% for Obinutuzumab compared with 33% for Rituximab was reported; however, results were not statistically significant, and no difference in PFS was observed between the groups after a median follow-up of 32 months. The safety profile with similar in both arms except infusion related toxicity and cough which was more frequent in Obinutuzumab arm.

As with Rituximab, results with Obinutuzumab have been more promising when the mAb is combined with chemotherapy. In the phase Ib Gaudi study, patients with relapsed or refractory FL were randomized to one of two arms: Obinutuzumab with chop (G-chop) or with Fludarabine–cyclophosphamide [13]. Overall, patients achieved ORRs of 96% with G-chop and 93% with Obinutuzumab–Fludarabine–Cyclophosphamide. In addition, all patients with Rituximab-refractory disease achieved at least a partial response. Neutropenia was the most common treatment-related toxicity, occurring in 43% of patients receiving g-chop and in 50% of those receiving Obinutuzumab–Fludarabine–Cyclophosphamide.

The efficacy of Obinutuzumab in Rituximab-refractory disease was explored further in the phase III Gadolin study, in which patients with Rituximab-refractory indolent NHL received either Obinutuzumab–Bendamustine (GB) induction followed by maintenance with Obinutuzumab, or Bendamustine monotherapy induction and no maintenance [13]. In that study, no statistical difference in ORR was observed between the groups after induction; however, patients in the (GB) group were more likely to be negative for minimal residual disease (82% vs. 43%, $p < 0.0001$)20. After a median follow-up of 21.9 months, treatment with (GB) was associated with superior PFS (not reached vs. 14.9 months with Bendamustine monotherapy, $p = 0.0001$)13 [14]. Grades 3 and 4 toxicities occurring more frequently with (GB) included neutropenia (33% vs. 26%).

Ongoing phase III combination therapy studies with Obinutuzumab include GALLIUM (first-line advanced iNHL; NCT01332968) and GOYA (first-line DLBCL; NCT01287741). GALLIUM aims to assess the efficacy and safety of Obinutuzumab plus chemotherapy versus Rituximab plus chemotherapy followed by maintenance immunotherapy. After induction, responders will progress to maintenance therapy with their randomized antibody treatment alone, given every 2 months until disease progression or for a maximum of 2 years. In May 2016, at a prespecified interim analysis, the GALLIUM independent Data Monitoring Committee recommended analysis of the study data as the primary endpoint of investigator-reported PFS had been met [15]. This is the second head-to-head comparative trial against Rituximab that has shown a positive result for Obinutuzumab, the first being the CLL11 study.

Following the results of GALLIUM trial, Obinutuzumab was approved by FDA at the time of writing of this article, as a first line treatment for follicular lymphoma.

Conclusion

Type II anti CD20 is following the trace of type I anti CD20 in both mode of action and trial designation. After approval of Rituximab in the first line setting in the treatment of FL, we witness the emerging role of Obinutuzumab replacing Rituximab. The ORR was 86.9% in R-chemo compared with 88.5 % in G-chemo with a complete response (CR) to be better in R-chemo arm 23.8% vs 19.5 % in G-chemo [16]. Though the difference is not enough to convince scientists worldwide to put Obinutuzumab in the first line, however: statistics are sufficient to make their hands prescribe the new promising agents.

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