

USE OF OBINUTUZUMAB FOR B-CELL MALIGNANCIES

Authors:

Mita Manna

Carolyn J Owen

*University of Calgary, Tom Baker
Cancer Centre, Division of Hematology
and Hematological Malignancies,
Calgary, Alberta, Canada*

Correspondence details:

Mita Manna, MD FRCPC, Lymphoma
Fellow, Division of Hematology and
Hematological Malignancies South
Tower Rm 601, Foothills Medical
Centre

Calgary, AB, T2N 2T9

Tel: 403-944-1993

Fax: 403-270-7891

Email:

Mita.Manna@albertahealthservices.ca

Carolyn Owen, MD, MDres(UK),
FRCPC, Associate Professor Division of
Hematology and Hematological
Malignancies South Tower Rm 603,
Foothills Medical Centre

Calgary, AB, T2N 2T9

Tel: 403-944-3265

Fax: 403-944-8352

Email:

Carolyn.Owen@albertahealthservices.ca

Abstract

We analysed data for the use of obinutuzumab in the treatment of CD20-positive lymphoproliferative disorders including chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphomas (NHL). Marked progress in the outcomes of B-cell NHL came with the development of targeted therapy against CD20 with the monoclonal antibody rituximab. Despite the benefit seen with rituximab, many patients relapse or become refractory after rituximab-containing therapies. This led to the development of more effective anti-CD20 monoclonal antibodies such as obinutuzumab. Several Phase III studies have been conducted comparing rituximab to obinutuzumab in patients with B-cell NHL. Obinutuzumab is a glycoengineered Type II anti-CD20 monoclonal antibody. An overview of the recently presented and/or published Phase III studies investigating obinutuzumab in the treatment of NHL and CLL are presented. The CLL11 Phase III study was the first study demonstrating the superiority of obinutuzumab over rituximab. Recently, several other Phase III studies have demonstrated improved outcomes for CLL and NHL with the use of obinutuzumab. Further evaluation, longer follow-up, and future studies investigating combination therapy with novel agents are warranted to demonstrate if obinutuzumab should replace rituximab as the standard of care.

Keywords: antibody, CD20, chronic lymphocytic leukemia, non-Hodgkin lymphoma, obinutuzumab

Disclosures: Honoraria and clinical trial participation and payments from Hoffman La Roche.

1. Introduction

Non-Hodgkin Lymphoma (NHL) is a relatively common malignancy accounting for approximately 4% of all cancers. Marked progress in the outcomes of B-cell lymphoma came with the development of the chimeric anti-CD20 monoclonal antibody rituximab. Rituximab was the first successful modality of targeted therapy in lymphoma, especially given that over 90% of B-cell NHLs express CD20.(1)

Outcomes have vastly improved in terms of progression-free (PFS) and overall survival (OS) since the development of rituximab.(2–4) However, despite the significant benefit of rituximab in the treatment of NHL, over 30% of patients either fail to respond or relapse after rituximab-containing therapies. This led to attempts at developing more effective targeted therapies for NHL.

A number of novel anti-CD20 monoclonal antibodies have been developed and have demonstrated efficacy in the treatment of NHL. The majority are Type I antibodies, like rituximab, which act mostly via complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.(5) A second class of monoclonal antibodies are classified as Type II antibodies. Obinutuzumab (GA101, Gazyva) is a glycoengineered Type II anti-CD20 monoclonal antibody that results in more potent direct cell death and has higher levels of antibody-dependent cellular cytotoxicity but less complement-dependent cytotoxicity than rituximab. Given superior outcomes compared to rituximab in a Phase III clinical trial in combination with chlorambucil, obinutuzumab is FDA-approved as frontline therapy for chronic lymphocytic leukemia (CLL).(6) Details of the pharmacology and mechanism of action of obinutuzumab were described in a previous review.(7) The objective of this review is to summarize the recently presented and/or published studies

investigating obinutuzumab in the treatment of NHL and CLL.

2. Clinical Studies

2.1. Phase I/II

Several Phase I/II studies have been performed in patients with relapsed/refractory CD20-positive NHL demonstrating efficacy and safety of obinutuzumab.(8–10) A randomised Phase II study was performed in relapsed indolent CD20-positive NHL comparing single agent obinutuzumab followed by maintenance therapy compared to single agent rituximab followed by maintenance.(11) At the end of induction, the investigator-assessed overall response rates (ORR) for patients with follicular lymphoma was superior in those who received obinutuzumab compared to rituximab (44.6% vs. 33.3%; $p=0.08$). Obinutuzumab was generally well tolerated although more patients reported infusion-related reactions (IRR; 74% vs. 51%). Of note, treatment was discontinued due to adverse events in 8% receiving obinutuzumab (3 patients due to IRR) compared to 10% receiving rituximab (1 patient due to IRR). This was the first study directly comparing obinutuzumab against rituximab and given the favourable response rates for obinutuzumab, led to further investigation with Phase III studies.

2.2. Phase III

2.2.1. CLL

The German CLL Study Group CLL11 study was the first Phase III study reported assessing the efficacy and safety of obinutuzumab in previously untreated CLL patients. The study included an elderly population of patients with comorbidities and enrolled 781 patients who were randomised to receive chlorambucil, obinutuzumab-chlorambucil, or rituximab-chlorambucil.(6) The results of the study

demonstrated an advantage in terms of ORR, with more complete remissions (CR), and improved PFS with the addition of an anti-CD20 monoclonal antibody (obinutuzumab or rituximab) to chlorambucil monotherapy. Median PFS was 26.7 months for obinutuzumab-chlorambucil vs. 11.1 months for chlorambucil alone, and 16.3 months for rituximab-chlorambucil vs. 11.1 months for chlorambucil alone. Additionally, an OS advantage was noted in the obinutuzumab-chlorambucil arm compared to the chlorambucil monotherapy arm ($p=0.002$), while no such difference was demonstrated with the addition of rituximab to chlorambucil ($p=0.11$). Obinutuzumab-chlorambucil was also superior to rituximab-chlorambucil with a statistically significant and clinically important improvement in PFS (26.7 vs. 15.2 months; $p<0.001$) and a trend towards an OS advantage (hazard ratio, 0.66; $p=0.08$). Furthermore, obinutuzumab-chlorambucil treatment was also shown to result in deeper responses with impressive rates of minimal residual disease (MRD) negativity compared to rituximab-chlorambucil treatment (bone marrow, 19.5% vs. 2.6%; peripheral blood 37.7% vs. 3.3%). Finally, obinutuzumab demonstrated an acceptable safety profile in comparison to the other arms.

The updated results of the CLL11 study were recently analysed after a median observation time of 42.4 months.(12) The updated data continues to show improved PFS with obinutuzumab-chlorambucil compared with rituximab-chlorambucil (median PFS 29.2 vs. 15.4 months; $p<0.001$). No statistically significant OS benefit was demonstrated for obinutuzumab-chlorambucil over rituximab-chlorambucil ($p=0.0632$); however, the OS benefit of obinutuzumab-chlorambucil over chlorambucil alone was confirmed ($p=0.0014$). Furthermore, rituximab-

chlorambucil treatment also demonstrated an OS benefit compared to chlorambucil alone ($p=0.0242$) after this extended follow-up period. These updated results confirm the efficacy of obinutuzumab plus chlorambucil in CLL.

Although obinutuzumab has an acceptable safety profile, it is associated with an increased rate of IRRs and a significantly higher rate of Grade 3-4 IRRs compared to rituximab. In the CLL11 study, 69% had IRRs of any grade in the obinutuzumab-chlorambucil arm compared to 39% in the rituximab-chlorambucil arm and grade 3-4 IRRs occurred in 20% of patients in the obinutuzumab-chlorambucil arm compared to 4% in the rituximab-chlorambucil arm.(6) All IRRs for obinutuzumab occurred during the first infusion of cycle one. Given the increased incidence of IRRs seen with obinutuzumab, the ongoing Phase IIIb GREEN study was aimed to investigate the safety and efficacy of obinutuzumab and to assess methods to reduce the incidence of IRRs.(13) The study compared the safety and efficacy of obinutuzumab monotherapy to obinutuzumab in combination with chemotherapy (bendamustine, fludarabine plus cyclophosphamide, or chlorambucil) in patients with previously untreated or relapsed/refractory CLL. A lower starting dose (12mg) and slower infusion rate (12.5mg/hour) was administered on Day 1 in the first cohort within the study to address the problem with IRRs. A preliminary analysis was presented in 2014 and focused on IRRs in 158 previously untreated patients. The median age of patients was 65 years, most with Binet stage B or C disease. IRRs occurred in 47.7%, 56.5%, 37.5%, and 61.1% and Grade 3-4 IRRs occurred in 10.5%, 17.4%, 0%, and 22.2 in those receiving obinutuzumab-bendamustine, obinutuzumab-fludarabine-cyclophosphamide, obinutuzumab-chlorambucil, and obinutuzumab monotherapy respectively.

Similar to previous studies, all IRRs occurred during the first administration of obinutuzumab in cycle one. The safety data were in line with the known safety profile of obinutuzumab and no new safety signals were noted; and there were similar numbers of discontinuations during cycle 1 observed with a total of 5.7% discontinuing therapy after cycle 1 with obinutuzumab monotherapy or in combination with chemotherapy despite the modified administration techniques. Therefore, IRRs continue to be a safety concern with the use of obinutuzumab with no method yet shown to confidently reduce the incidence or severity of first infusion IRRs. As a result, a second cohort of the GREEN study will receive a dose of dexamethasone 12 hours prior to obinutuzumab infusion with a goal of reducing the incidence of first-infusion IRRs. The final results from this study are eagerly awaited.

A subgroup analysis of the GREEN study was also presented at the American Society of Hematology Annual Meeting in 2015, focusing on the obinutuzumab-bendamustine treated cohort.(14) Stilgenbauer and colleagues analyzed the safety and efficacy of obinutuzumab-bendamustine in previously untreated patients with CLL. The analysis included 158 patients, of which 74 were fit and 84 were unfit; the median age was 67.6 years. The safety data were in line with the known safety profile of obinutuzumab and common grade 3-5 adverse effects included neutropenia (50%), infection (12.7%), thrombocytopenia (12.7%), and tumor lysis syndrome (10.1%). The ORR was 78.5% with a CR rate of 32.3%. MRD negativity was observed in 58.9% in blood, and 27.8% in bone marrow. The authors' conclusions were that the obinutuzumab-bendamustine combination in previously untreated CLL has an acceptable safety profile with a high rate of CRs and MRD negativity offering a

promising treatment option for patients with CLL.

2.2.2 *Indolent NHL*

Results from the planned interim efficacy and safety analysis of the Phase III GALLIUM study were recently presented at the American Society of Hematology Annual Meeting in 2016.(15) This study was performed in patients ≥ 18 years with previously untreated NHL, comparing obinutuzumab-based induction and maintenance to rituximab-based induction and maintenance. The primary endpoint was investigator-assessed PFS. Patients included in the study had previously untreated follicular lymphoma (grades 1-3a) or marginal zone lymphoma, and required treatment as per the Group d'Etude des Lymphomes Folliculaires Criteria (GELF) criteria. Patients were randomised to receive induction chemo-immunotherapy consisting of obinutuzumab or rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or bendamustine, followed by maintenance antibody in responding patients. Patients received rituximab $375\text{mg}/\text{m}^2$ on day 1 of each cycle or obinutuzumab 1000mg on days 1, 8, and 15 of cycle 1 and day 1 of subsequent cycles. A total of 1202 patients were enrolled (601 received obinutuzumab-chemotherapy and 601 received rituximab-chemotherapy). Only the results for the patients with follicular lymphoma were presented. At the end of induction, the investigator-assessed ORR was 86.9% for the obinutuzumab-treated patients and 88.5% for the rituximab-treated patients. After a median follow-up of 34.5 months, the investigator assessed 3-year PFS was 80.0% for obinutuzumab and 73.3% for rituximab, with a HR of 0.66 ($p=0.001$). This equated to an estimated 3-year improvement in PFS in the obinutuzumab

arm, assuming a 6-year median PFS for the rituximab group. 3-year OS, however, was similar between both arms. Patients in the obinutuzumab group experienced more grade 3-5 adverse events including neutropenia (43.9% vs. 37.9%), febrile neutropenia (6.9% vs. 4.9%), infections (20.0% vs. 15.6%), and IRRs (12.4% vs. 6.7%); however, the frequency of fatal adverse events were similar (4.0% vs. 3.4%). The authors' conclusions were that these data support an obinutuzumab-based induction and maintenance regimen to become the new standard of care in previously untreated patients with follicular lymphoma.

A second presentation reported the results of MRD analysis from the GALLIUM study.(16) MRD was assessed at mid induction (MI) and at the end of induction (EOI) in 1101 follicular lymphoma patients enrolled in the GALLIUM study using quantitative RT-PCR for t(14:18) and clonal immunoglobulin heavy-chain variable rearrangement. Molecular response rates in both obinutuzumab-based and rituximab-based regimens were high at MI (94.3% vs. 88.9%) and at EOI (92% vs. 85%), with a higher proportion of patients achieving MRD-negativity at MI and EOI in the obinutuzumab-based regimen. MRD kinetics showed a faster and deeper response with obinutuzumab. Interestingly, the chemotherapy backbone in the rituximab-based regimen affected MRD status at EOI with rituximab-bendamustine, giving higher MRD response rate compared to rituximab-CHOP and rituximab-CVP. No effect was seen in the obinutuzumab-based arm with MRD status similarly high between the three chemotherapy regimens. Future analysis of MRD kinetics during maintenance/follow-up is ongoing and should provide information on the prognostic value of MRD status in predicting relapse.

Finally, the open-label, multicenter, randomised Phase III GADOLIN study compared the efficacy and safety of obinutuzumab plus bendamustine induction followed by obinutuzumab maintenance compared with single agent bendamustine induction in rituximab-refractory indolent NHL patients.(17) The median number of prior therapies was two and most patients were refractory to their previous regimen. After a median follow-up of 21.9 months in the obinutuzumab-bendamustine arm and 20.3 months in the bendamustine monotherapy arm, the median PFS was significantly longer in the obinutuzumab-bendamustine arm compared to the bendamustine arm (median not reached vs. 14.9 months; $p=0.0001$). Updated results were recently presented at the American Society of Hematology Annual Meeting in 2016 with a median follow-up of 31.8 months. The investigator-assessed PFS was 25.8 months in the obinutuzumab-bendamustine arm compared to 14.1 months in the bendamustine monotherapy arm, equivalent to a 43% relative reduction in risk of progression or death for the obinutuzumab arm.(18) A significant improvement in OS was also seen in the obinutuzumab arm (76% vs. 63%; $p=0.006$). Adverse effects remained comparable in each arm and no new safety signals were noted. Previous studies noted higher frequency of neutropenia, infection, and IRRs with obinutuzumab compared to rituximab in this patient population.(6) The authors' conclusions were that obinutuzumab-bendamustine improves PFS and OS in rituximab-refractory iNHL.

2.2.3 Aggressive NHL

Obinutuzumab was also investigated in the Phase III GOYA study in patients with previously untreated diffuse large B- cell lymphoma (DLBCL), randomizing patients to obinutuzumab-CHOP versus rituximab-CHOP (R-CHOP). R-CHOP is

standard of care in these patients, however approximately 30% fail to achieve a remission or relapse after this rituximab-based therapy.(19) The primary endpoint of investigator-assessed PFS demonstrated no significant difference between obinutuzumab-CHOP and rituximab-CHOP (3-year PFS, 69% vs. 66%). Furthermore, there was no significant improvement in PFS by cell of origin or treatment arm, leading to the conclusion that obinutuzumab is not superior to rituximab in patients with previously untreated DLBCL.(20)

3. Conclusion

Obinutuzumab is a novel anti-CD20 Type II monoclonal antibody that has demonstrated efficacy and safety in the treatment of NHL and CLL based on Phase III clinical trials. The CLL11 study established the superiority of obinutuzumab over rituximab in the treatment of therapy-naïve CLL patients with co-morbidities. The GALLIUM and GADOLIN studies demonstrated superiority of obinutuzumab over rituximab in terms of PFS in patients with previously untreated and rituximab refractory FL, respectively. Obinutuzumab appears to have similar toxicity to rituximab; however, IRRs, particularly high grade IRRs, are more frequent with obinutuzumab during the first infusion.

Despite the introduction of emerging novel therapies for CLL, such as Bruton tyrosine kinase inhibitors, phosphatidylinositol-3 kinase inhibitors, BCL-2 family anti-apoptotic protein inhibitors, and Type I and II anti-CD20 monoclonal antibodies, CLL remains an incurable disease. Given obinutuzumab's proven efficacy in CLL, many studies are currently underway investigating combination therapy with obinutuzumab and novel agents, including the Bcl-2 inhibitor venetoclax (ABT-199), the Bruton's tyrosine kinase (BTK) inhibitor

ibrutinib, and the more selective irreversible BTK inhibitor acalabrutinib.

The results of the GALLIUM study demonstrate an improvement in PFS with obinutuzumab over rituximab though no improvement in OS, and slightly more frequent, though manageable toxicity. Further longer term follow-up is necessary to clarify the extent of the PFS benefit and to assess for any impact on OS. Several investigators have questioned whether differences in outcomes and toxicity of obinutuzumab over rituximab may be attributable to the higher administered dose and intensity of obinutuzumab. This question will likely not be directly answered with a well-controlled study of obinutuzumab versus high dose rituximab. Although improved response rates were observed with higher doses of rituximab monotherapy in a small, uncontrolled study of CLL patients, combination chemoimmunotherapy with higher doses of rituximab did not result in improved outcomes.(21,22) The results from the GADOLIN study demonstrate that obinutuzumab has clear value for patients who fail to respond or have early relapse following rituximab-chemotherapy.

Since the introduction of rituximab, combination chemoimmunotherapy has revolutionized the treatment of CD20 positive lymphoproliferative disorders with improved response rates and more durable remissions. Novel agents continue to be developed with a goal of further improving survival. The new approval of a subcutaneous (SC) formulation of rituximab should make the administration of rituximab cheaper and more tolerable. The SABRINA study was a phase III study comparing intravenous (IV) to SC rituximab in patients with untreated follicular lymphoma. Results demonstrated the pharmacokinetic profile of SC rituximab was non-inferior to IV rituximab, and that ORR was similar

between IV and SC rituximab post-induction therapy.(23) Thus, SC rituximab appears to enable a more convenient method of delivery with comparable efficacy to IV rituximab. SC rituximab is now approved in Europe for both NHL and most recently for patients with previously untreated and relapsed/refractory CLL. Future studies comparing SC rituximab to obinutuzumab would be required to assess safety and efficacy between these agents.

In conclusion, obinutuzumab is a novel anti-CD20 Type II monoclonal

antibody that has demonstrated safety and efficacy in patients with CLL and NHL in several Phase III studies. Further evaluation and longer follow-up is warranted to demonstrate if obinutuzumab should replace rituximab as the standard of care in all patients with these diseases. Furthermore, future studies investigating combination of obinutuzumab with other novel agents may give rise to improved response rates and remissions.

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