Obinutuzumab for the treatment of non-Hodgkin lymphomas

AUTHORS
Juana Hernandez, Tina Nielsen, Christian Klein, Michael Wenger

AFFILIATION
F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070, Basel, Switzerland

F Hoffmann-La Roche Ltd (Roche) has a rich history of research and development of antibody therapies to treat cancers (malignancies) that affect B cells (a type of white blood cell), including non-Hodgkin lymphoma and chronic lymphocytic leukaemia. While dependent on the type of cancer and the stage when the cancer is diagnosed, the outcomes for patients with B-cell malignancies are generally poor and require further improvement.

INDOLENT NON-HODGKIN LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKAEMIA

Non-Hodgkin lymphomas can be classified according to the speed at which they progress. Those that grow and spread slowly are described as 'indolent', one of the most common types of which is follicular lymphoma. About one-fifth of new cases of non-Hodgkin lymphoma are diagnosed as follicular lymphoma[1]. Follicular lymphoma usually appears as painless, slowly growing lymph nodes. In the early stages of disease there are typically no symptoms, but at advanced stages the patient may experience symptoms such as fever, night sweats, weight loss and general lack of energy. The disease is typically characterised by a series of relapses and retreatment. Often, with each relapse, the disease becomes increasingly resistant to chemotherapy[2].

Chronic lymphocytic leukaemia is the most common type of adult leukaemia in the Western world. Most patients are diagnosed when a high number of blood lymphocytes are found after a patient has a full blood count for an unrelated reason. In common with follicular lymphoma, chronic lymphocytic leukaemia is slow to progress. Many patients do not have symptoms for years, but if the treating physician notices a sharp increase in the number of lymphocytes and a drop in the number of red blood cells, they may begin treatment.

These chronic diseases contrast with the aggressive non-Hodgkin lymphoma subtype, diffuse large B-cell lymphoma, which can be fatal within weeks or months of diagnosis if not treated. Diffuse large B-cell lymphoma and treatment advances for diffuse large B-cell lymphoma are described further in this issue of *Nature Outlook: Lymphoma.*

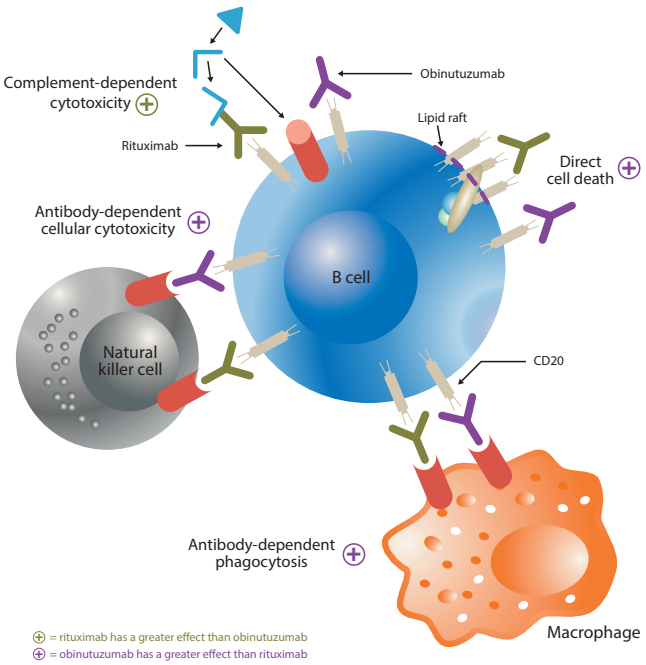

Figure 1: Differences in the proposed mechanisms of action of rituximab and obinutuzumab. Rituximab is a type I antibody that functions by the stabilisation of CD20 on lipid rafts, resulting in strong complement-dependent cytotoxicity. Obinutuzumab is a glycoengineered type II antibody that leaves CD20 distributed across the surface of the B cell and has much lower complement-dependent cytotoxicity, but greater antibody-dependent cellular cytotoxicity, antibody-dependent phagocytosis and direct cell death.

IMMUNOTHERAPIES FOR NON-HODGKIN LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKAEMIA

Immunotherapies are often described as 'biological' or 'targeted' therapies that stimulate the body's immune system to act against cancer cells. In the search for an immunotherapy for B-cell malignancies, the membrane protein CD20 was considered a prime target. CD20 is found on the surface of all normal B cells and on 95% of cancerous B cells.

Rituximab, developed in partnership by Roche and Biogen Idec, was the first anti-CD20 monoclonal antibody to be approved for the treatment of non-Hodgkin lymphomas. It works by specifically targeting the CD20 protein and kills B cells in three different ways: 1) antibody-dependent cellular cytotoxicity –'effector' immune cells such as natural killer cells and macrophages are recruited to kill the B cells, including the cancerous B cells; 2) complement-dependent cytotoxicity – the proteins of the 'complement' system are recruited, which damage the B-cell membrane leading to cell

death; and 3) direct cell death – as rituximab binds to the B cell through the CD20 receptor, the signal causes the B cell to die[3]. These mechanisms are shown in more detail in Figure 1. Rituximab in combination with chemotherapy was found to be effective at destroying both cancerous and healthy B cells; when the rituximab treatment is completed, the body replaces the normal B cells.

In 1997, rituximab received approval for use by the United States Food and Drug Administration (US FDA) for the treatment of patients with relapsed low-grade non-Hodgkin lymphomas. It was the first therapeutic antibody to be approved for chronic lymphocytic leukaemia and non-Hodgkin lymphoma. Compared with the previously available chemotherapy treatments, rituximab improved the survival outlook for these patients. One study showed that after a median observation period of 18 months, patients with advanced stage follicular lymphoma who received rituximab in combination with chemotherapy were significantly less likely to experience treatment failure than patients who received chemotherapy alone[4].

THE UNMET MEDICAL NEED FOR FOLLICULAR LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKAEMIA

Although rituximab helps many patients with non-Hodgkin lymphoma and chronic lymphocytic leukaemia, and was a major step forward in the treatment of the disease, it has some limitations. The level and duration of the response to rituximab may decrease over time. Eventually, the majority of patients receiving rituximab relapse and some even develop resistance to the drug. In addition, some patients do not respond to initial rituximab treatment, or their disease continues to get worse while receiving rituximab[5]. Furthermore, while patients with indolent diseases survive for a comparatively long time, on average between six and ten years with treatment, they usually cannot be cured if they present in the clinic in the advanced stages of disease. Also, at some stage their disease may become more aggressive. Consequently, Roche has continued to develop new treatments to improve upon rituximab for these patient populations.

OBINUTUZUMAB, A HUMANISED, GLYCOENGINEERED, TYPE II, MONOCLONAL ANTIBODY

Roche wanted to create an antibody that would overcome some of the limitations of rituximab and be more effective than rituximab at treating B-cell malignancies. Roche used a process known as glycoengineering to design obinutuzumab. Glycoengineering involves controlling the type of sugar molecules in the Fc region of the antibody. The Fc region of the antibody recruits immune cells to kill the target cell, which is bound by the antibody. Laboratory testing of obinutuzumab showed that compared with rituximab, the Fc region of obinutuzumab is more effective at recruiting effector immune cells (antibody-dependent cellular cytotoxicity and phagocytosis) and thus better at triggering the death of cancerous cells (**Fig. 1**). Obinutuzumab was the first medicinal product using glycoengineering technology to be approved in the US and the European Union (EU)[6]. Obinutuzumab is a type II antibody, unlike rituximab, which is a type I antibody. These classifications are based on the way the antibodies bind to CD20. When rituximab binds to CD20, it reorganises the CD20 molecules on the cancerous B cells into lipid rafts, which indirectly triggers cell death by a mechanism known as complement-dependent cytotoxicity (**Fig. 1**). In contrast, the type II antibody, obinutuzumab, is not as effective at inducing complement-dependent cytotoxicity but is much more effective than rituximab at inducing direct cell death. This direct action of obinutuzumab on B-cell death, together with its effective induction of antibody dependent cellular cytotoxicity and antibody-dependent phagocytosis, may represent an important advantage, as it has the potential to reduce the risk of drug resistance seen with rituximab.

CLINICAL TRIALS OF OBINUTUZUMAB

The superior effects of obinutuzumab seen in the laboratory have been confirmed in clinical trials and, in 2013, the drug was the first drug to be awarded Breakthrough Therapy Designation by the US FDA. Obinutuzumab was compared with rituximab in stage 2 of the CLL11 clinical trial of patients with chronic lymphocytic leukaemia and other co-existing conditions; both groups also received chlorambucil chemotherapy[7]. The use of obinutuzumab in the CLL11 trial led to a 51% decrease in the risk of disease worsening or death compared with rituximab. The trial also showed that patients who received obinutuzumab survived for longer than those who received rituximab; the risk of death was 24% lower in the obinutuzumab group compared with the rituximab group (**Fig. 2**). The side effect profiles of rituximab and obinutuzumab were similar, although the number of patients experiencing side effects, including reactions during or following drug infusions, and a decrease in some blood cell counts (neutrophils), was higher in those treated with obinutuzumab compared with rituximab.

A phase III study, called the GADOLIN trial, looked at the risk of disease worsening or death in patients with indolent non-Hodgkin lymphoma who did not respond to, or who relapsed during or within 6 months after a previous rituximab treatment regimen. These patients received either obinutuzumab plus chemotherapy (bendamustine) or bendamustine only. Patients who received the obinutuzumab regimen were 43% less likely to experience disease worsening or death than those who received chemotherapy only. This trial also showed that 75% of patients in the group who received obinutuzumab survived to the end of the study, compared with only 65% of the patients receiving chemotherapy alone; this represented a 33% lower risk of death in the group of patients who received obinutuzumab (**Fig. 2**)[8]. The side effects experienced by patients in the GADOLIN study were similar for both treatment groups. The findings from GADOLIN led to the US approval of obinutuzumab in combination with bendamustine chemotherapy, followed by obinutuzumab alone, as a new treatment regimen for patients with follicular lymphoma who relapse after rituximab treatment, or who do not respond to rituximab. Shortly after, obinutuzumab in combination with bendamustine was approved in the EU for patients with follicular lymphoma who do not respond to rituximab or who relapse within six months of rituximab treatment.

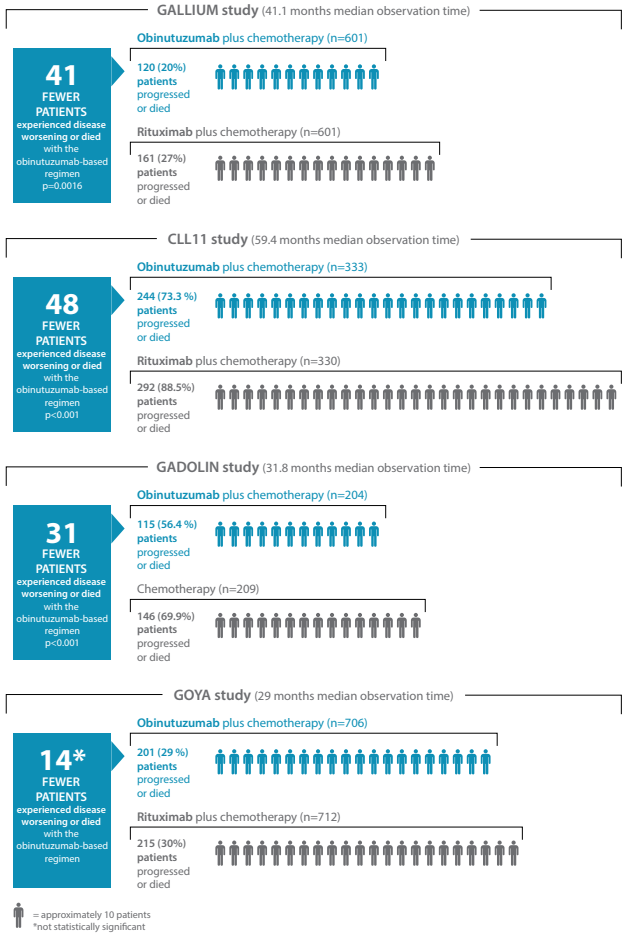

Figure 2: Reduction in the risk of disease worsening and death in four key clinical trials of obinutuzumab. The GALLIUM trial compared obinutuzumab plus chemotherapy combinations with rituximab plus chemotherapy in patients with previously untreated follicular lymphoma[9]. The CLL11 trial compared obinutuzumab plus chemotherapy (chlorambucil), with rituximab plus chlorambucil in patients with chronic lymphocytic leukaemia. GADOLIN compared obinutuzumab plus chemotherapy (bendamustine) with bendamustine alone in patients with indolent non-Hodgkin lymphoma who did not respond to rituximab[8]. GOYA compared obinutuzumab plus chemotherapy combinations with rituximab plus chemotherapy in patients with previously untreated advanced-stage diffuse large B-cell lymphoma[10].

Roche also investigated the use of obinutuzumab for indolent non-Hodgkin lymphoma patients who have not previously received treatment. The GALLIUM clinical trial assessed the efficacy of obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy in patients with previously untreated follicular lymphoma. In this trial, the risk of disease worsening or death was 32% lower in patients who received obinutuzumab compared with those who received rituximab[9]. Obinutuzumab was more effective than rituximab but the group receiving obinutuzumab had a different profile of side effects. Importantly, the improvement in patient quality of life was similar with obinutuzumab and rituximab, despite the different side effects[9]. The outcomes of the GALLIUM trial led to the approval, in the US, EU and many other countries, of obinutuzumab in combination with chemotherapy for the treatment of patients with previously untreated advanced follicular lymphoma.

Disappointingly, the results of the GOYA trial of obinutuzumab in patients with the aggressive form of non-Hodgkin lymphoma, diffuse large B-cell lymphoma, revealed that outcomes with obinutuzumab were not better than with rituximab when combined with chemotherapy[10]. Diffuse large B-cell lymphoma is the most common type of non-Hodgkin lymphoma making up about 30% of all lymphomas. It is typically fatal if left untreated and so more effective drugs for patients with diffuse large B-cell lymphoma are desperately needed. The search for such treatments by Roche has uncovered a new antibody-drug conjugate, polatuzumab vedotin, described in this edition of *Nature Outlook: Lymphoma.*

FUTURE DIRECTIONS

Roche continues to look at ways of advancing the treatment of lymphomas. One approach is to combine obinutuzumab with different drugs, including chemotherapy-free treatment options. A programme of early phase clinical studies, known as InHarmony, is testing obinutuzumab combinations with various different drugs that have different mechanisms of action in different groups of patients with lymphoma (either those receiving their first treatment or those who have relapsed following treatment). Such combinations include an immunomodulatory agent (lenalidomide), a checkpoint inhibitor (atezolizumab), a Bcl2 inhibitor (venetoclax) or an antibody-drug conjugate (polatuzumab vedotin).

An ongoing study (CLL14) of patients with previously untreated chronic lymphocytic leukaemia is comparing the efficacy of obinutuzumab in combination with the drugs venetoclax or chlorambucil. Roche is dedicated to improving the lives of patients with non-Hodgkin lymphoma and chronic lymphocytic leukaemia. A number of additional approaches to the treatment of B-cell malignancies are in the pipeline, including the T cell bispecific antibodies, mosunetuzumab[11] and CD20-TCB[12]. Our aim is to optimise the use of available treatments while continuing to search for new, more effective treatments for these life-limiting diseases.

ACKNOWLEDGEMENT

Third-party medical writing assistance, under the direction of the authors, was provided by Angela Rogers of Gardiner-Caldwell Communications, and was funded by F. Hoffmann-La Roche Ltd.

REFERENCES

1. The Non-Hodgkin's Lymphoma Classification Project. *Blood* **89**, 3909–3918 (1997).
2. Montoto, S. *et al. Ann. Oncol.* **13**, 523–530 (2002).
3. Freeman, C. L. & Sehn, L. H. *Br. J. Haematol.* **182**, 29–45 (2018).
4. Hiddemann, W. *et al. Blood* **106**, 3725–3732 (2005).
5. Cartron, G., Trappe, R. U. *Clin. Cancer Res.* **17**, 19–30 (2011).
6. Mössner, S. *et al. Blood* **115**, 4393–4402 (2010).
7. Goede, V. *et al. N. Eng. J. Med.* **370**, 1101-1110 (2014).
8. Cheson, B. *et al. J. Clin. Oncol.* **36**, 2259–2266 (2018).
9. Hiddemann, W. *et al. J. Clin. Oncol.* **36**, 2395–2404 (2018).
10. Vitolo, U. *et al. J. Clin. Oncol.* **35**, 3529–3537 (2017).
11. Sun, L. L. *et al. Sci. Transl. Med.* **7**, 287ra70 (2015).
12. Bacac, M. *et al. Clin. Cancer Res.* **24**, 4785-4797 (2018).