Non-Hodgkin lymphoma: Treatment advances for diffuse large B-cell lymphoma

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F Hoffmann-La Roche Ltd (Roche) was founded in Basel, Switzerland, in 1896. Since then, Roche has grown into one of the world's leading healthcare companies. With over 100 years of experience, we have driven progress and innovation in healthcare and pride ourselves as being pioneers in the development of new treatments for cancer.

Harnessing an increasing body of knowledge in the field of immunology, and applying technological advances in recombinant DNA developed from the 1950s to the 1990s, Roche, in partnership with Biogen Idec, developed the first medically approved therapeutic monoclonal antibodies for the treatment of lymphoma (rituximab) and breast cancer (trastuzumab). Monoclonal antibodies are now routinely used to treat many cancers, and Roche continues to innovate in order to help patients with cancer to fight their disease.

Over the past 20 years our research has contributed to transforming the lives of patients with diseases of the blood, including non-Hodgkin lymphoma. We have a dedicated, ongoing programme of research, aimed at designing and developing new, more effective therapies for various subtypes of non-Hodgkin lymphoma. In this article we provide an overview of the work being carried out by Roche to further improve the prospects for patients with aggressive forms of this often-fatal disease.

AT ROCHE WE ARE DRIVEN BY OUR PASSION FOR UNDERSTANDING THE BIOLOGY OF DISEASE, AND BY OUR DESIRE TO DO MORE FOR PATIENTS.
– NANCY VALENTE, VP, GLOBAL PRODUCT DEVELOPMENT ONCOLOGY AND HEAD OF HEMATOLOGY DEVELOPMENT AT ROCHE.

NON-HODGKIN LYMPHOMA

White blood cells, called T and B lymphocytes (B and T cells) help protect the body from infection. In cancerous lymphocytic diseases, there is a rapid proliferation of malignant lymphocytes. The malignant lymphocytes tend to collect in lymph nodes, causing them to swell and form cancerous tumours. There are many different types of non-Hodgkin lymphoma and the response of patients to treatment depends largely on the type of lymphoma and the stage at which it is diagnosed. Some lymphomas grow and spread slowly (described as 'indolent'), for example follicular lymphoma and marginal zone lymphoma. Others are faster growing ('aggressive'), for example, diffuse large B-cell lymphoma, Burkitt's lymphoma and mantle cell lymphoma.

ROCHE'S HERITAGE IN NON-HODGKIN LYMPHOMA TREATMENT

Rituximab is a therapeutic antibody, designed using both human and mouse genes, and has been licensed since 1997 for the treatment of several types of non-Hodgkin lymphoma, including follicular lymphoma, previously untreated diffuse large B-cell lymphoma and chronic lymphocytic leukaemia. In combination with other drugs, rituximab has become the standard of care for several types of non-Hodgkin lymphoma. However, despite improvements in the clinical outcomes of patients due to advances in treatments such as rituximab, indolent B-cell malignancies remain incurable, as do approximately half of aggressive lymphomas. A need exists for treatments that can significantly improve the duration of treatment response and extend patients' lives.

In order to help patients with non-Hodgkin lymphoma and other patients with malignant diseases of the blood, Roche designed a new therapeutic antibody called obinutuzumab. Obinutuzumab is a fully humanised, glycoengineered antibody, approved for the treatment of follicular lymphoma and previously untreated chronic lymphocytic leukaemia, and is discussed in more detail in this issue of *Nature Outlook: Lymphoma.*

Roche is continuing this strong heritage in the development of novel antibody therapies for patients with B-cell malignancies by developing new treatments such as bispecific antibodies, which can bind to two different targets at the same time (most therapeutic antibodies bind to a single target). Mosunetuzumab and RO7082859 are two bispecific antibodies currently in development by Roche. These bispecific antibodies are designed to engage and activate T cells to kill malignant B cells.

In addition, Roche is focusing on new treatments for patients with the most common type of non-Hodgkin lymphoma – diffuse large B-cell lymphoma. For patients with this type of lymphoma, approximately 40% do not respond to initial treatment

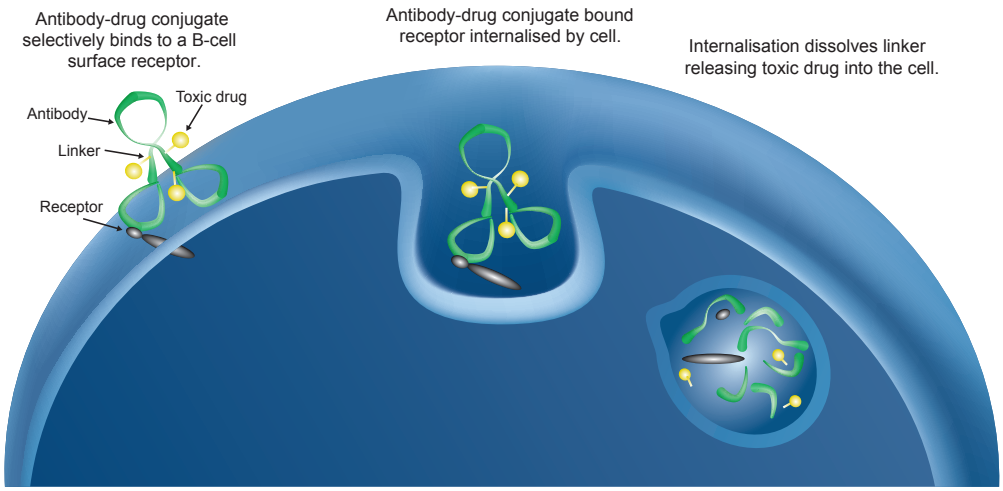

Figure 1: The proposed mechanism of action of antibody-drug conjugates. The antibody–drug conjugate selectively binds to the protein receptor on the surface of B cells. The antibody–drug conjugate and receptor are rapidly taken into a part of the cell that contains enzymes known as a lysosome. The small protein that links the toxic drug to the antibody is broken down by enzymes and the cytotoxic drug is released into the cell, leading to cell death.

or become resistant to therapy; currently, there is very little that can be done for such patients. Roche has begun to address this unmet need with a class of treatment called an antibody-drug conjugate, which may have the potential to improve outcomes.

DIFFUSE LARGE B-CELL LYMPHOMA – AN AGGRESSIVE FORM OF NON-HODGKIN LYMPHOMA

Diffuse large B-cell lymphoma is a cancer of the B cells in the blood and globally represents about 30—58% of cases of non-Hodgkin lymphoma[1]. It is by far the most common type of aggressive non-Hodgkin lymphoma and is fatal within weeks or months if left untreated[2]. The first symptom of diffuse large B-cell lymphoma is often a painless swelling in the groin, armpit or neck caused by enlarged lymph nodes; swellings can grow quickly, sometimes over a period of weeks. Other symptoms include tiredness, weight loss, night sweats and high temperatures. This type of lymphoma mainly affects older people over the age of 50 years, but it can also affect children and younger adults.

TREATMENTS FOR DIFFUSE LARGE B-CELL LYMPHOMA

The current recommended initial treatment for diffuse large B-cell lymphoma is a combination of drugs: rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone, often abbreviated to R-CHOP. While the combination R-CHOP achieves moderate success for these patients (around 60% will be cured), still approximately 30—40% of patients either do not respond to R-CHOP or relapse following treatment; most relapses happen within 2 years[3]. For patients who do not respond or relapse following treatment with R-CHOP, there is limited success with currently available treatments. One treatment option is high-dose chemotherapy and stem cell transplant. However, due to advancing age or other health-related issues, only approximately half of patients are eligible for treatment with this intensive therapy. For patients who are not eligible for transplant, treatment options are limited and most will die from their disease in a matter of weeks or months[3].

ROCHE'S ANTIBODY-DRUG CONJUGATE, POLATUZUMAB VEDOTIN

Antibody-drug conjugates are a class of drugs comprising an antibody, which is bound to a cytotoxic agent by a linker that is stable in the circulation but degrades when inside the target cell. The antibody is targeted to an antigen present on a specific cell type. Intravenous administration of the antibody–drug conjugate results in its binding to the target antigen on the surface of the cell, and internalisation into the cell. Upon internalisation, the cellular environment digests the linker releasing the cytotoxic payload into the target cell (**Fig. 1**).

Roche is investigating an antibody–drug conjugate, polatuzumab vedotin, for the treatment of diffuse large B-cell lymphoma. Polatuzumab vedotin, created in collaboration with Seattle Genetics, (Bothell, Washington, United States) is composed of a CD79b-specific monoclonal antibody conjugated to a microtubule-disrupting agent called monomethyl auristatin E by a stable linker. CD79b is a transmembrane protein expressed on the surface of B cells as part of the B-cell receptor complex and is abundant on the tumours of patients with diffuse large B-cell lymphoma[4,5]. Polatuzumab vedotin is currently being tested in several clinical trials.

There is much more work to be done in testing new therapeutic antibodies for non-Hodgkin lymphoma and the treatment of patients with diffuse large B-cell lymphoma is a priority area of research for Roche. Our goal is to extend the lives of all patients with non-Hodgkin lymphoma, including diffuse large B-cell lymphoma.

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