

How the discovery of rituximab impacted the treatment of B-cell non-Hodgkin's lymphomas

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INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is the sixth-most common cancer in the UK, accounting for around 13,700 new cases every year. Until the late 1990s, treatment relied on intensive chemotherapy, such as CHOP (cyclophosphamide–doxorubicin HCl–vincristine [Oncovin]–prednisone). The use of standard CHOP therapy and its variations had resulted in poor five-year survival rates (as low as 26%), particularly in patients with aggressive NHL, such as diffuse large B-cell lymphoma (DLBCL).

Rituximab (Rituxan) was the first chimeric (mouse/human) monoclonal antibody approved for the treatment of NHL. It was approved by the US Food and Drug Administration in 1997 for indolent forms of NHL. It subsequently received EU approval in June 1998, and was licensed under the trade name Mabthera (Roche, Basel, Switzerland). It then went on to be approved for the first-line treatment of aggressive forms of NHL, such as DLBCL (to be used in combination with CHOP or other anthracycline-based chemotherapy) in 2006. It is directed against the CD20 protein, an antigen found on the surface of B-cell lymphomas. With minimal toxicity, activity as a single-agent (for indolent forms of NHL) and safety when combined with chemotherapy, it represents great progress in this field.

Here, I discuss how this antibody therapeutic was developed from basic molecular and cellular considerations through to preclinical and clinical evaluations and how it came to be a first-line treatment for NHL, and improving treatment outcomes for patients with DLBCL compared with the pre-rituximab era.

NHL IN THE PRE-RITUXIMAB ERA

Five percent of all newly diagnosed malignancies are lymphomas, with diagnosis of NHL (90% of lymphomas) based on the absence of Reed-Sternberg cells. It is the most common haematological cancer in adults, with around 13,700 patients being diagnosed in the UK every year.¹

The use of standard CHOP therapy and its variations in the pre-rituximab era was able to achieve complete responses (CRs) in only 40%–50% of elderly patients. Three-year event-free and overall survival (OS) rates were as low as 30% and 35%–40%, respectively.² Efforts to increase the efficacy of CHOP through the addition of other cytotoxic agents had failed: no significant improvements in disease free survival and OS were found. This may be due to the fact these agents could not be administered unless the cyclophosphamide and doxorubicin dosages were lowered to below that given in the standard CHOP treatment.^{18,20} In addition, CHOP was more cost-effective and had less toxicity than the more complex CHOP-containing regimens. Despite failed attempts to increase efficacy, CHOP continued to be the gold standard of DLBCL treatment.

As such, the best therapy option available until the 1990s was unable to cure >50% of patients with aggressive lymphomas (and most patients with low-grade lymphomas).³ This was coupled with the steadily rising incidence of NHL throughout the 1970s and 1980s, particularly in the elderly. By the 1990s, NHL accounted for one in 30 cases of and one in 40 deaths from cancer, with around 2,400 male and 2,200 female deaths.⁴ Therefore, there was a desperate need for new approaches to treatments with different mechanisms of action and improved toxicity profiles.

Rituximab is directed against the CD20 antigen, and was approved by the US FDA in 1997 and the EMA in 1998, for use in selective B-cell-depletion therapy (Fig 1).

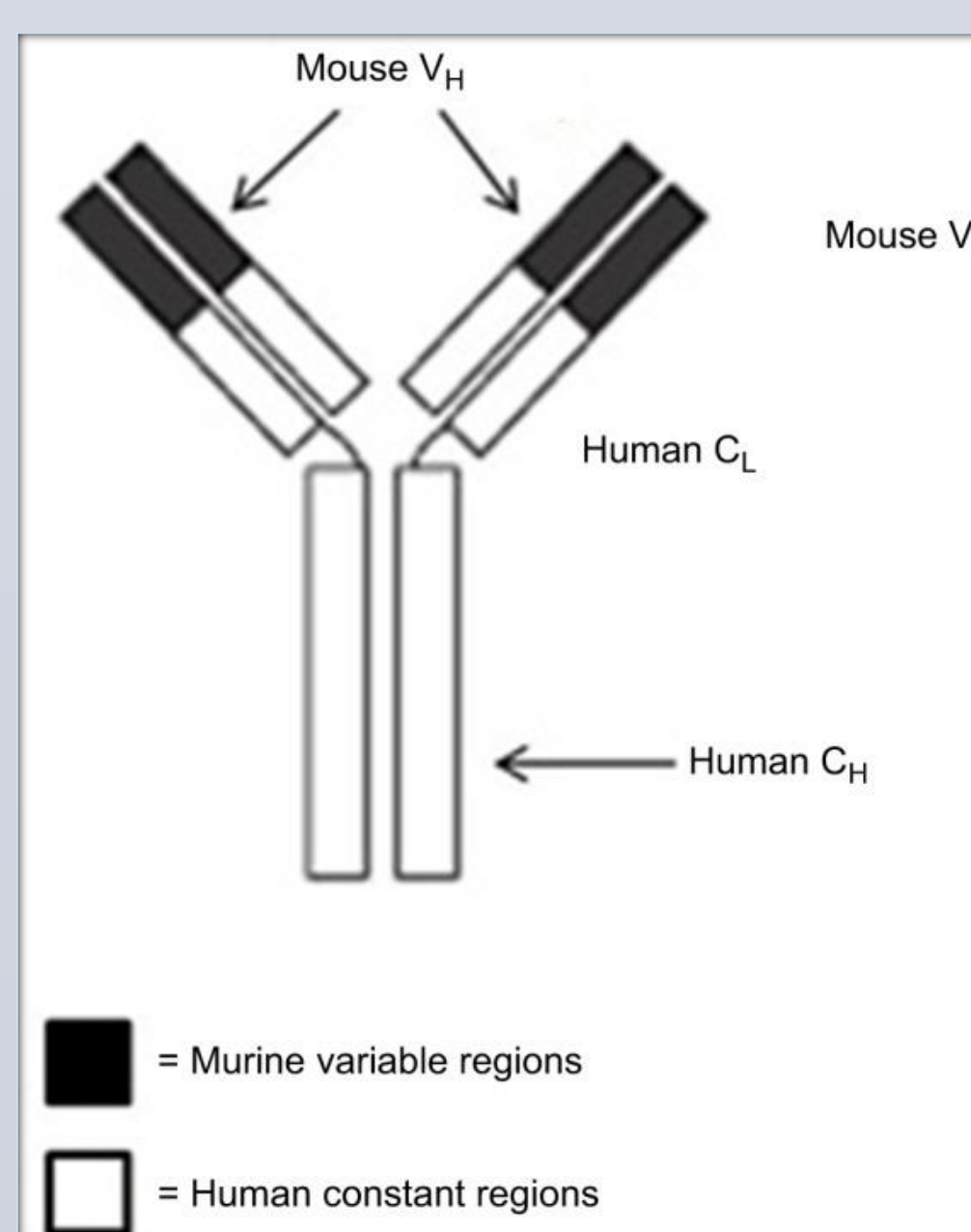


Fig 1: Structure of rituximab, a chimeric monoclonal antibody (~30% mouse origin and ~70% human origin).

IMPACT OF RITUXIMAB

Rituximab binds to the CD20 antigen via its Fab domain, and the Fc domain recruits immunoeffector functions involved in B-cell lysis. Evidence suggests it stabilizes CD20 on lipid rafts, which promotes ADCC. This is mediated by Fcγ receptors on the surface of granulocytes, macrophages, and NK cells. Other postulated mechanisms include complement-dependent cytotoxicity activated by C1q binding and the subsequent lytic cascade, as well as apoptosis (Fig 2).⁵

Previously, DLBCL treatment had been severely restricted to CHOP before the advent of rituximab. However, its use had resulted in poor 5-year survival rates for patients with aggressive NHL – as low as 26%.⁶ Rituximab approval was granted by the FDA for first-line treatment of DLBCL in combination with CHOP or other anthracycline-based chemotherapy regimens in February 2006.⁷ Approval was granted based on the results of a successful phase III randomized clinical trial comparing R-CHOP to CHOP alone in aggressive lymphomas (Table 1).

The results from these prospective trials were very promising, as the addition of rituximab to chemotherapy showed a clear benefit in patient outcomes. Until 2014, only a handful of population-based, retrospective analyses had been carried out that assessed rituximab's impact on survival of patients with DLBCL. These register-based analyses provided data comparing the outcome of patients who had been administered CHOP or R-CHOP, and confirmed that R-CHOP had a positive effect.

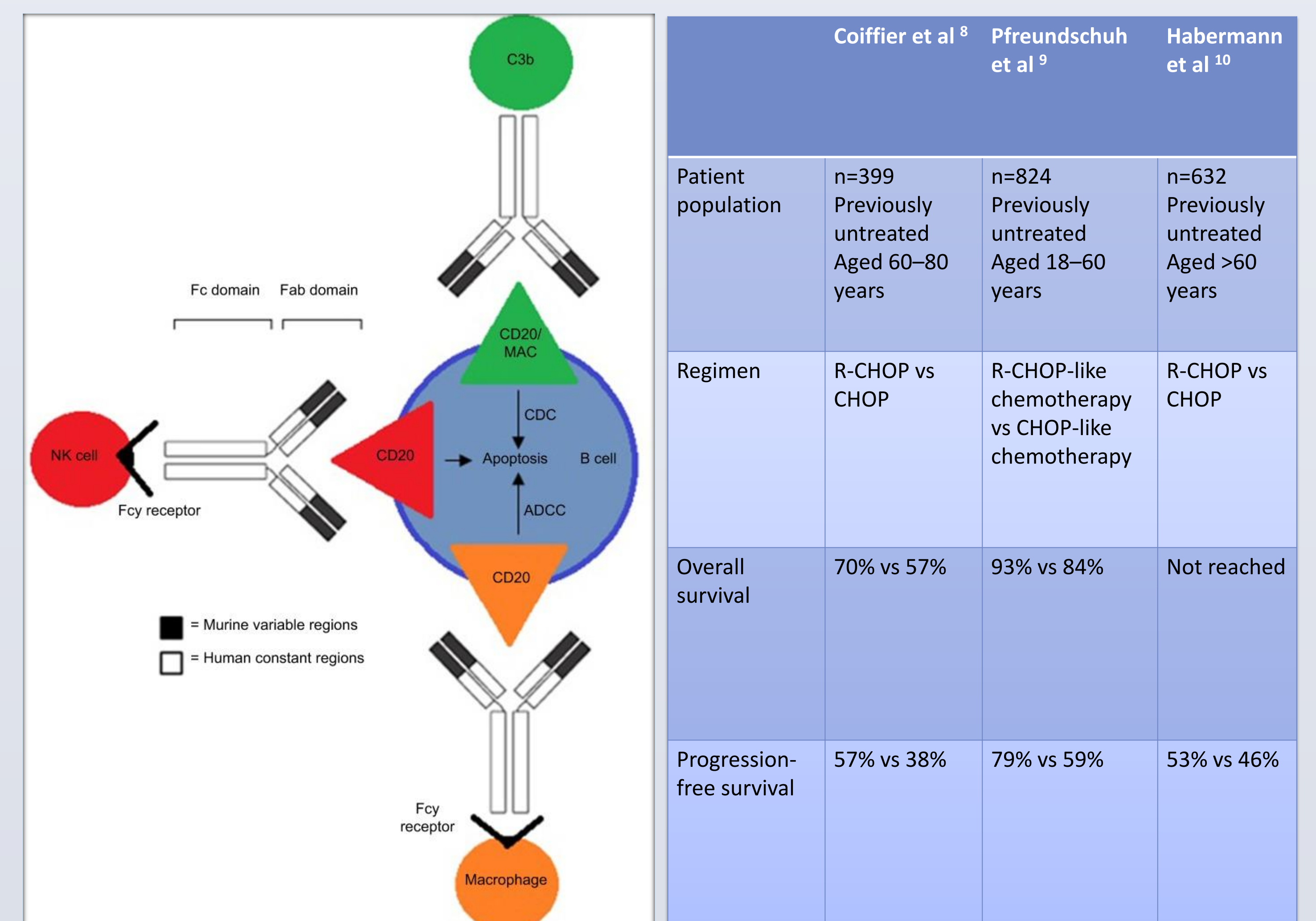


Fig 2: The MoA Rituximab uses to kill B cells associated with NHL through binding of the CD20 antigen. Table 1: Trials led to US Food and Drug Administration (FDA) approval for its use in this context.

CONCLUSION

Over 20 years of clinical use later, the R-CHOP chemotherapy (every 14 or 21 days) remains a first-line treatment for DLBCL, and it is probable that it will remain an integral component of therapy regimens. The clear impact rituximab has had on treatment outcomes for B-cell NHLs cannot be disputed. It is safe and well tolerated in all age-groups. Prognosis of DLBCL has improved significantly in the last decade due to these treatments being implemented, although earlier or more precise diagnosis also plays a role. However, relapse is still an issue for DLBCL patients: over 30% of patients fail to respond to current treatment regimens or suffer relapse. In addition, the high cost per course of Rituximab remains a significant barrier to its widespread use, and alternative toxin-conjugated anti-CD20 therapy (such as Rituximab-Doxorubicin) and NFκB-inhibitors (such as Bortezomib), may change the treatment paradigms and outcomes for B-cell lymphomas.

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