Review

A Review of Anti-CD20 Antibodies in the Management of B-Cell Lymphomas

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Abstract: Anti-CD20 monoclonal antibodies (mAbs) have revolutionized the treatment of lymphomas by improving the survival of patients, particularly in conjunction with chemotherapy. Until recently, the gold standard was based on the utilization of Rituximab (RTX) combined with chemotherapy. With our better understanding of monoclonal antibody (mAb) engineering, anti-CD20 mAb therapy has evolved to enhance clinical outcomes by improving pharmacokinetics, safety, activity and immunogenicity. Efforts to improve the on-targeting CD20 expressed on lymphomas through novel bioengineering techniques have led to the development of newer anti-CD20 mAbs that have accentuated complement-dependent cytotoxicity (CDC), antibody-dependent cell medicated cytotoxicity (ADCC), and/or a direct killing effect. There are several anti-CD20 monoclonal antibodies that have been evaluated for the treatment of lymphomas, some of which are now approved in addition to RTX.

Keywords: CD20; rituximab; non-Hodgkin's lymphoma (NHL); follicular lymphoma (FL); diffuse large B-cell lymphoma (DLBCL); Ofatumumab; Obinutuzumab

1. Introduction

Anti-CD20 antibodies strategically bind to B-cells positive for CD20, a surface transmembrane protein marker [1]. Their ability to bind to CD20 markers and activate the direct signaling of apoptosis, facilitate complement activation and subsequent complement-mediated cytotoxicity (CDC), as well as induce antibody-induced cell-mediated cytotoxicity (ADCC) through natural killer (NK) cells, plays an integral role in the treatment options for various lymphomas [1,2].

Non-Hodgkin's lymphoma (NHL) has several subtypes—follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL) are typically indolent, meanwhile diffuse large B-cell lymphoma (DLBCL) is aggressive. The common feature amongst them is the malignant B-cell and its surface protein, CD20. Thus, antibodies that target CD20 have been pertinent in the evolution of NHL treatment [2,3].

Rituximab (RTX), a monoclonal antibody (mAb) against CD20, has been widely used for lymphoma therapy [3]. It has been in use for more than two and a half decades and has extensive clinical safety data. The most common adverse effect (AE) is an infusion-related reaction (IRR) and symptoms typically include fever and skin rash and may occasionally culminate in hypotension, shock or arrhythmias [4]. Another common AE is B-cell lymphopenia, which leads to an increased incidence of infections that are generally controlled by humoral immune responses [4].

RTX in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) remains the standard frontline regimen for DLBCL [3]. Obinutuzumab, another humanized mAb against CD20, has undergone glycoengineering and has distinctive

mechanistic properties. Obinutuzumab in combination with bendamustine is approved for relapsed/refractory (R/R) FL patients treated with an RTX-containing regimen as well as the frontline treatment of FL [5]. Anti-CD20 antibodies are seldom used as monotherapy currently in CLL and are mostly used in conjunction with Bruton tyrosine kinase inhibitors (BTKi) or venetoclax. In this review, we delineate the various anti-CD20 antibodies that are approved as well as the ones currently undergoing evaluation for the management of B-cell lymphomas. A brief comparison of newly FDA-approved anti-CD20 antibodies with RTX is given in Table 1.

Table 1. A brief comparison of newly approved anti-CD20 antibodies with rituximab.

Comparison Factors	Rituximab (RTX)	Ofatumumab	Obinutuzumab
Bioengineering-related mechanistic change	- Chimeric monoclonal antibody; - Binds to a discontinuous epitope within the extracellular domain of CD20 [2].	- Second-generation human anti-CD20 antibody; - Binds to a separate epitope from RTX which includes a small extracellular loop and N terminal region of the second large extracellular loop, leading to greater binding avidity [6]; - Binds closer to the cell membrane [7].	- Third-generation humanized anti-CD20 antibody; - Caspase-independent direct cytotoxicity [8]; - C1q binding property [9].
Proposed difference in therapeutic action	- Binds to CD20 on B-cells and induces CDC, ADCC and ADCP, as well as direct apoptosis [2].	- Enhanced ADCC and CDC compared to RTX. Action sustained even with low levels of CD20 [6,7].	- Enhanced direct cytotoxicity [8]; - Superior ADCC and ADCP - Inferior CDC [9].
Efficacy—Follicular lymphoma	Reference mAb—RTX	Comparable outcomes to RTX—PFS (16.33 vs. 21.29 months; not significant) and ORR (50% vs. 66%) compared to RTX [10].	- Has shown superior outcomes compared to RTX—ORR 88.5% vs. 86.9%: 3-year PFS 80.0% vs. 73.3% and HR for progression, relapse, or death = 0.66 [11].
Efficacy—Diffuse large B-cell lymphoma	Reference mAb—RTX	- Failed to establish superiority over RTX—2-year mPFS and mOS were 24% and 41% for O-DHAP, respectively versus 26% and 38%, respectively for R-DHAP [12].	- Failed to establish superiority over RTX—5-year PFS was 63.8% in the G-CHOP arm vs. 62.6% in the R-CHOP arm [13]; - Exploratory endpoint analysis showed greater benefit in the germinal center B-cell subtype [13].
Efficacy—Chronic lymphocytic leukemia	Reference mAb—RTX	- Higher in vitro efficacy; - Limited clinical data showing higher efficacy compared to RTX [14].	- Higher efficacy in terms of PFS, CR and molecular response rates [15,16].
Efficacy—Mantle cell lymphoma	Reference mAb—RTX	- Higher in vitro and in vivo efficacy demonstrated in pre-clinical models compared to RTX [17].	- Superiority over RTX in pre-clinical models [16].
Adverse effect profile	Reference mAb—RTX	- Higher incidence of adverse events including serious adverse events (infections, cardiac events, neoplasms) compared to RTX [10,12]; - Higher incidence of infusion-related reactions compared to RTX [10,12].	- Higher incidence of adverse events including serious adverse events (infections, cardiac events, neoplasms) compared to RTX [11,13]; - Higher incidence of infusion-related reactions compared to RTX [11,13].

CDC—complement-dependent cytotoxicity, ADCC—antibody-dependent cell-mediated cytotoxicity, ADCP—antibody-dependent cell-mediated phagocytosis, ORR—objective response rate, PFS—progression-free survival, CR—complete remission, CHOP—cyclophosphamide, doxorubicin, vincristine and prednisone, Ab—monoclonal antibody.

2. Resistance to RTX and the Bioengineering of Newer Anti-CD20 Antibodies

Despite the widespread use of RTX, the mechanisms by which RTX resistance is conferred have not been clearly delineated. One theory is that continuous exposure exhausts the store of complement proteins, thus conferring resistance due to a depletion of the necessary effector molecules [18]. Klepfish et al. infused fresh frozen plasma (FFP) in conjunction with RTX into treatment-refractory CLL patients and found rapid and dramatic clinical responses in all patients [18]. A study from Xu et al. lends further support to this theory, as they reported similarly positive results when combining FFP with RTX [18]. Pederson et al. described a process of shaving, wherein RTX-CD20 complexes are shed off from cells by phagocytes, thus inducing refractoriness [19]. Wang et al. found that RTX-resistant cell lines demonstrated apoptosis resistance, in particular, due to the hyperactivated NF-kB pathway and Bcl2 overexpression [20]. Czuczman et al. supported this theory, reporting that constant RTX exposure resulted in a downregulation of the pro-apoptotic proteins Bax and Bak [21].

This led to the development of second-generation anti-CD20 antibodies like Ofatumumab, Ocrelizumab and Veltuzumab and third generation anti-CD20 antibodies like Obinutuzumab, Ocaratuzumab, EMAB-6 and Ublituximab. Ofatumumab was one of the first newer anti-CD20 monoclonal antibodies to receive FDA approval for CLL. It is a second-generation, type 1 human IgG$_1$k antibody [22]. It binds to a separate epitope from RTX, which includes a small extracellular loop and N terminal region of the second large extracellular loop, leading to greater binding avidity, which has been proposed to lead to enhanced ADCC [6]. Ofatumumab has also shown a better CDC than RTX, likely because it can bind closer to the cell membrane than RTX. Even with a low expression of CD20, the immune activity, its CDC particularly seems to be sustained [7]. Obinutuzumab is a third-generation humanized anti-CD20 antibody that has been FDA-approved for various lymphomas [16]. Obinutuzumab is an Fc-glycoengineered type 2 anti-CD20 antibody with greater direct cytotoxicity (believed to be caspase-independent) than RTX [8]. It has also shown superiority over RTX in ADCC and antibody-dependent cellular phagocytosis (ADCP) while being substantially inferior in its CDC, probably due to its C1q binding properties [9,23]. Figure 1 delineates the approval timeline of all three anti-CD20 antibodies in various lymphomas and Figure 2 depicts the binding of these antibodies to specific epitopes on the CD-20 receptor protein and their functional effects.
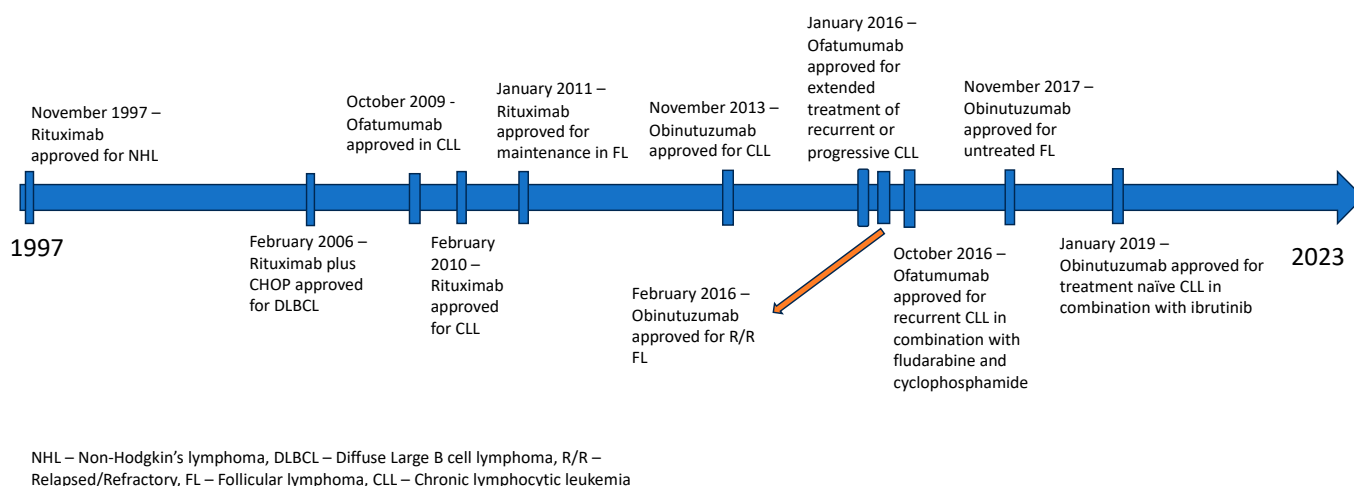

NHL – Non-Hodgkin's lymphoma, DLBCL – Diffuse Large B cell lymphoma, R/R – Relapsed/Refractory, FL – Follicular lymphoma, CLL – Chronic lymphocytic leukemia

Figure 1. FDA approval timeline of anti-CD20 antibodies in various lymphomas.
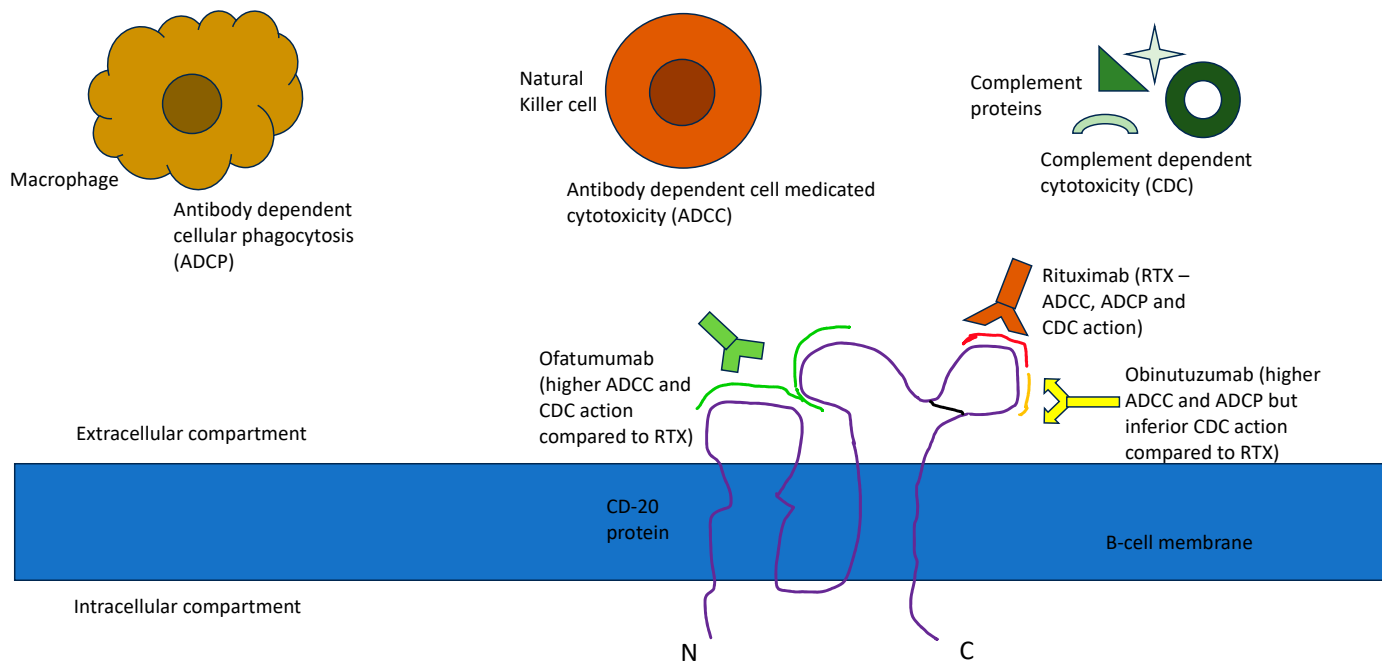
Figure 2. CD20 epitope binding and functional effect of anti-CD20 antibodies.

3. Follicular Lymphoma (FL) and Other Indolent Non-Hodgkin's lymphomas (NHLs)

A phase 2 trial of an RTX monotherapy in 166 patients with R/R low-grade NHL demonstrated an objective response rate (ORR) of 48% and was well tolerated with manageable toxicity. This led to the regulatory approval of RTX by the US FDA [24]. Ofatumumab was compared with RTX in patients with FL and it failed to show superiority [10]. The GALLIUM phase 3 trial showed the superiority of Obinutuzumab over RTX in terms of its PFS and ORR. However, it also showed increased adverse events, including infusion reactions, compared to RTX [5].

A total of 46 patients with low-tumor burden FL after front-line RTX induction therapy were followed for 83.9 months. The median progression-free survival (mPFS) was 23.5 months and the median overall survival (mOS) was 91.7%. This trial showed that a majority of patients had a durable response to RTX [25]. A phase 3 trial evaluated rituximab maintenance therapy for up to 5 years after RTX induction in FL and showed that there was no difference in event-free survival (EFS) or OS [26]. RTX was evaluated in combination with CHOP therapy (R-CHOP) in 38 patients with treatment-naïve as well as previously treated low-grade NHL. The ORR was 100% and 87% achieved a complete response (CR). The median time to progression was 82.3 months. This study showed the substantial potential of RTX plus chemotherapy in low-grade NHL [27]. Another prospective study of R-CHOP vs. CHOP showed that the addition of RTX reduced the relative risk for treatment refractoriness by 60% ($p < 0.001$). The overall response rate was substantially higher (96% vs. 90%; $p = 0.011$) and a prolonged duration of remission ($p = 0.001$) was also noted [28].

Failure-free survival (FFS) is defined as the time interval between the reference date (date of randomization or date of diagnosis, etc.) and the date of progression/relapse at local, regional or metastatic sites. EFS is defined as the time from randomization until disease progression, not including surgery, local or distant recurrence, or death of any cause. The ECOG 1496 and PRIMA trials evaluated RTX maintenance therapy after induction with RTX plus chemotherapy in treatment-naïve FL and showed a significant increase in the 3-year PFS (ECOG 1496—64% vs. 33%; HR 0.4, $p < 0.001$), (PRIMA—74.9% vs. 57.6% HR 0.55, $p < 0.001$) [29,30]. The PFS benefit was sustained even after 6 years in the PRIMA study (59.2% vs. 42.7%; HR 0.58, $p = 0.0001$) [31].

RTX along with fludarabine, cyclophosphamide and mitoxantrone (FCM) showed superior responses in R/R FL compared to FCM alone in a phase 3 study [32]. Furthermore,

maintenance with RTX led to a higher durability of the response [33]. A similar pattern was demonstrated in a phase 3 trial evaluating R-CHOP vs. CHOP, where the addition of RTX as part of induction therapy and subsequent maintenance therapy with RTX led to accentuated clinical outcomes in R/R FL [34]. An individual patient data meta-analysis evaluating RTX maintenance therapy included seven randomized trials with 2315 FL patients in total and showed that a higher OS was achieved compared to observation (HR 0.79, 95% CI 0.66–0.96) for all patients with FL except the subgroup which received RTX during induction [35]. The role of RTX in FL patients with a low disease burden compared to active surveillance remains to be determined [36]. A study by Sohani et al. evaluated tissue samples from four anti-CD20 therapy-based phase 2 trials and showed that interfollicular BCL6 positivity, interfollicular CD10 positivity and Ki67 $\geq$ 30% within neoplastic follicles was correlated with a worse PFS at 2 years.

A phase 1/2 study showed promising results for ofatumumab in RTX R/R FL with an ORR of 43% [37]. This prompted a phase 3 randomized controlled trial (RCT) (HOMER) comparing Ofatumumab to RTX in indolent B-cell NHLs that had relapsed after RTX-based therapy [10]. The patient population comprised RTX-sensitive relapsed FL that relapsed at least 6 months after completing the last treatment. The Ofatumumab arm had a shorter PFS (16.33 vs. 21.29 months; statistically not significant) and lower ORR (50% vs. 66%, not significant) compared to the RTX arm. IRR (2% vs. 0%, respectively), pneumonia (<1% vs. 2%, respectively) and sepsis (<1% vs. 1%, respectively) were the most frequently reported serious AEs (SAEs). IRRs (82% vs. 51%), infection-related AEs (32% vs. 37%), cardiac events (7% vs. 4%), neoplasms (6% vs. 3%) and mucocutaneous reactions (58% vs. 22%) were higher in the ofatumumab arm than the rituximab arm [10]. A recent single-center phase 1/2 trial studied Ofatumumab in combination with bendamustine, carboplatin and etoposide (BOCE) in 35 patients with relapsed/refractory NHL [38]. The ORR was 69% while the median PFS and OS were 5.1 and 26.2 months, respectively, with no treatment-related deaths. Twelve patients subsequently underwent allogeneic hematopoietic cell transplantation (ASCT). The authors concluded BOCE to be a safe and effective outpatient regimen for R/R NHL patients while awaiting transplantation [38].

A phase 1 study involving 21 heavily pretreated R/R CD20+ indolent NHL showed encouraging results (5/21 CR; 4/21 PR; 43% ORR) for Obinutuzumab [39]. A randomized phase 2 study, GAUSS, compared Obinutuzumab to RTX in 175 patients with relapsed CD20+ indolent B-cell NHL (149 patients with FL histology and 26 patients with non-FL histology) [40]. The results showed an increased ORR (43.2% vs. 38.7% in FL and 43.2% vs. 35.6% overall) for Obinutuzumab compared to RTX without any additional safety concerns [40]. Another phase 2 study, GAUGUIN, evaluating obinutuzumab in 40 patients with R/R indolent NHL (34 patients with FL histology) also showed encouraging results (ORR 55%; mPFS 11.9 months) without additional safety concerns [41]. Together, these studies showed promising results for the use of obinutuzumab in FL. Another study, GAUDI, explored the safety and efficacy of obinutuzumab combined with chemotherapy (G-CHOP or G-FC) in 56 patients with R/R FL [42]. The ORR and CR for G-CHOP were 96% and 39%, respectively while they were 93% and 50%, respectively for G-FC [42]. Both regimens demonstrated an acceptable safety profile with no new AEs detected [42]. This led to the phase 3 RCT, GALLIUM, comparing 1000 mg Obinutuzumab vs. 375 mg/m^2 RTX plus chemotherapy as the first-line therapy in 1202 patients with FL [5]. At a median follow-up of 34.5 months, obinutuzumab showed superiority over RTX (ORR 88.5% vs. 86.9%; 3-year PFS 80.0% vs. 73.3%; and HR for progression, relapse, or death of 0.66) [5]. This study paved the way for its approval as the first-line in FL [11]. Grade 3–5 AEs (68% vs. 62%), serious AEs (38% vs. 32%) and IRR (11% vs. 6%) were higher in the obinutuzumab group. AEs leading to the cessation of treatment occurred in 97 patients (16.3%) in the Obinutuzumab group in comparison to 85 (14.2%) patients in the rituximab group [43]. Another phase 3 open-label RCT, GADOLIN, compared obinutuzumab plus bendamustine vs. bendamustine in RTX refractory indolent NHL [43]. The obinutuzumab arm showed an improved mPFS with an HR of 0.55 [43]. The final analysis from the GALLIUM trial

showed that after a median of 7.9 years of follow-up, PFS was higher with obinutuzumab plus chemotherapy vs. rituximab-based therapy, with 7-year PFS rates of 63.4% vs. 55.7%, respectively (p = 0.006). Serious adverse events were slightly higher with obinutuzumab (48.9%) compared to rituximab (43.4%). However, the rates of adverse events culminating in fatality were similar (4.4% and 4.5%, respectively). These data consolidated the long-term benefit of obinutuzumab-based therapy and reaffirmed its role as a standard of care for the first-line management of advanced FL [44].

4. Diffuse Large B-Cell Lymphoma (DLBCL)

R-CHOP was compared with CHOP alone in DLBCL and showed significantly accentuated outcomes in terms of the EFS, CR rates, OS and FFS with no new safety signals. Thus R-CHOP became the front-line therapy in the management of DLBCL. Even in the R/R setting, the outcomes with RTX plus chemotherapy were enhanced. Ofatumumab and obinutuzumab have also been approved for DLBCL but they failed to show superiority, in combination with chemotherapy, over RTX.

DLBCL is divided into two molecular subgroups—activated B-cell-like (ABC) and germinal center B-cell-like (GBC). It was initially subdivided into four genetic groups— MCD, BN2, N1 and EZB, which were based on which genes are rearranged or over-expressed [45]. Subsequently, two more subgroups were added—A53 (TP53 inactivation) and ST2 (SGK1 or TET2 mutations) [46]. In the R-CHOP era for treating DLBCL, the BCL2 rearrangement predicted an inferior OS among patients with the GCB subtype. BCL2 amplification correlates with an inferior OS and PFS within the ABC subtype. The effect of MYC rearrangements depends on a second genetic hit, particularly in BCL2, BCL6 or TP53. MYC overexpression determines the OS and PFS, however, other genetic aberrations modify its prognostic effect. BCL6 rearrangements negatively correlate with OS and PFS within the ABC subgroup [47].

A phase 2 trial evaluated RTX in combination with standard-dose CHOP in 33 patients with aggressive NHL (2/3rd were DLBCL). The ORR was 94% and CR was 61%. CR was observed irrespective of BCL-2 translocation. This trial was the first to demonstrate the benefit of combined R-CHOP in DLBCL [48]. These compelling results enabled phase 3 trials for this combination in DLBCL. One of them involved previously untreated elderly patients (aged 60–80 years) with DLBCL and randomized them to R-CHOP vs. CHOP therapy. The CR rate was significantly higher with R-CHOP (76% vs. 63%, p = 0.005). The 2-year EFS (57% vs. 38%; HR 0.58, p < 0.001) and 2-year OS (70% vs. 57%; HR 0.64, p = 0.007) were also accentuated with R-CHOP in comparison to CHOP therapy [49].

R-CHOP was subsequently compared to CHOP in younger patients with DLBCL (18–60 years) in a phase 3 trial. The 3-year EFS rate (79% vs. 59%; p < 0.0001), 3-year PFS rate (85% vs. 68%; p < 0.0001) and 3-year OS rate (93% vs. 84%; p = 0.0001) were higher with the addition of RTX compared to CHOP alone [50]. Long-term follow-up studies from all these trials showed that the benefit of R-CHOP was durable in both elderly and younger patients. The EFS (42% with R-CHOP vs. 25%: p = 0.0001) and PFS (52% vs. 29%, respectively: p = 0.0001) were significantly better for patients treated with combination therapy [51–53]. RTX monotherapy was also evaluated in the R/R setting for DLBCL and showed an encouraging response [54].

A phase 2 trial evaluating the safety and efficacy of Ofatumumab in 81 patients with relapsed/progressive DLBCL showed an ORR of 11%, mPFS of 2.6 months and median duration of response (DOR) of 9.5 months [55]. While the results were disappointing, it was not unexpected given the heavily pretreated population of the study. Another phase 2 study investigated Ofatumumab with either ifosfamide, carboplatin, etoposide (O-ICE) or dexamethasone, cytarabine, cisplatin (O-DHAP) in 61 patients with R/R DLBCL, grade 3b FL or transformed FL [56]. An ORR of 61% and CR of 37% showed that replacing RTX with ofatumumab was a promising approach [56]. Subsequently, a phase 3 RCT (ORCHARRD) compared O-DHAP to R-DHAP as salvage therapy in 447 patients with R/R DLBCL [12]. Patients who experienced a response to two cycles were given a third cycle followed by

high-dose chemotherapy (bischloronitrosourea, etoposide, cytarabine and melphalan) and ASCT. The ORR and CR for O-DHAP were 38% and 15%, respectively, compared to 42% and 22%, respectively, for R-DHAP. At 2 years, the mPFS and mOS were 24% and 41% for O-DHAP, respectively, versus 26% and 38%, respectively, for R-DHAP. Ultimately, there was no difference between the two treatment arms and O-DHAP failed to show superiority over R-DHAP. Grade 4 thrombocytopenia (35% vs. 35%, respectively) and neutropenia (22% vs. 26%, respectively) were similar across the treatment groups. The incidence of SAEs was similar between the treatment groups. The most common SAEs were febrile neutropenia (13%), acute kidney injury (5%), thrombocytopenia (5%) and nausea/vomiting (5%). Rash (22% vs. 9%, respectively) and increased serum creatinine (23% vs. 16%, respectively) were higher in the O-DHAP vs. R-DHAP group [12].

A phase 2 study, GATHER, evaluating Obinutuzumab + CHOP (G-CHOP) in 100 patients with untreated advanced DLBCL, showed that G-CHOP is clinically active with an acceptable safety profile [57]. This study gave some encouraging signs of breaking the R-CHOP ceiling in DLBCL. GOYA, a phase 3 RCT compared G-CHOP to R-CHOP as the first-line therapy in 1418 patients with untreated DLBCL [13]. The 5-year PFS was 63.8% in the G-CHOP arm (vs. 62.6% in the R-CHOP arm) [46]. Grade 3–5 AEs (75.1% vs. 65.8%), serious AEs (44.4% vs. 38.4%) and fatal AEs (6.1% vs. 4.4%) were all higher in the G-CHOP arm, with the most common fatal AEs being infections. A larger number of patients in the G-CHOP arm stopped any treatment component due to an AE (12.4%) compared to the R-CHOP arm (8.3%) [13]. In conclusion, G-CHOP failed to show any benefit over R-CHOP in untreated DLBCL, but an exploratory endpoint analysis showed some benefit in the germinal center B-cell subtype [13].

5. Chronic Lymphocytic Leukemia (CLL)

RTX in combination with chemotherapy like fludarabine and cyclophosphamide (FCR) showed superior outcomes compared to chemotherapy alone [58]. With the advent of newer targeted therapies like BTKi and venetoclax, RTX was tested along with these newer therapies and showed accentuated outcomes. Furthermore, with newer anti-CD20 antibodies on the horizon, venetoclax has been evaluated with obinutuzumab and showed superior outcomes compared to obinutuzumab plus chemotherapy [15]. Anti-CD20 antibody plus BTKis or venetoclax is regarded as one of the front-line therapies for CLL. The role of anti-CD20 monotherapy seems diminished.

In the CLL8 trial, FCR was compared to FC alone in previously untreated CLL patients. The mPFS was significantly prolonged with the combination therapy, along with OS, ORR and CR rates [59]. An updated analysis showed that the mPFS was almost twice as long with FCR compared to FC (56.8 months vs. 32.9 months; HR 0.59, $p < 0.001$) [58]. The REACH study compared FCR or FC in patients with previously treated CLL and showed a higher PFS with FCR (30.6 months vs. 20.6 months; HR 0.65, $p < 0.001$) [60]. Patients without the 17p or 11q deletions and with a mutated Ig heavy chain variable (IGHV) region gene achieved extremely durable responses [58]. The CLL10 trial compared RTX plus bendamustine (BR) vs. FCR in treatment-naïve robust CLL patients. FCR had a higher PFS than BR but this was primarily in the younger population [61]. Furthermore, BR had fewer adverse events, especially severe infections, than FCR [61]. This led to an understanding that FCR is a more efficacious regimen but that BR may have a role in robust elderly CLL patients. Another option for less robust untreated CLL patients is RTX plus chlorambucil. It was evaluated in a phase 2 trial which was well tolerated and had an ORR up to 84% [62]. RTX has also been evaluated as a maintenance therapy in elderly CLL patients who have received prior induction therapy with FCR. The PFS was significantly higher in patients who received RTX for two years compared to observation. However, it was associated with increased AEs [63]. RTX was further tested with the Bruton tyrosine kinase (BTKi) inhibitor, ibrutinib (I). The NCRI FLAIR trial evaluated this combination (IR) in comparison to FCR in treatment-naïve CLL patients and discovered that IR had a higher PFS with IGHV-unmutated CLL but had no difference in IGHV-mutated CLL. There was

no difference in OS between the two groups [64]. However, most patients received effective second-line treatment which may have contributed to the lack of difference in OS. Another phase 3 trial, E1912, compared IR vs. FCR and showed that IR had a superior PFS in both IGHV-mutated (HR: 0.27; $p < 0.001$) as well as unmutated (HR: 0.27; $p < 0.001$) patients. Furthermore, it had a higher OS (HR, 0.47; $p = 0.018$) compared to FCR [65]. Idelasib is a phosphoinositide 3-kinase (PI3K) delta inhibitor that has been tested in combination with RTX vs. RTX alone in R/R CLL patients. The combination showed an improved PFS and OS compared to RTX alone. However, there was an increased incidence of several AEs like diarrhea, colitis and pneumonia [66]. Ofatumumab was approved for use in CLL after compelling results in two studies. A phase 1/2 study of ofatumumab involved 33 patients with previously treated R/R CLL. The ORR was 48% with no CR. The mPFS was 106 days. Another phase 2 trial used ofatumumab in fludarabine- and alemtuzumab-refractory CLL and in fludarabine-refractory CLL with bulky (>5 cm) lymphadenopathy. The ORR was 58% and 47%, respectively. Ofatumumab was further approved for the extended treatment of CLL after another trial evaluated ofatumumab vs. observation and showed an mPFS benefit of 29.4 months vs. 15.2 months, respectively [14].

Venetoclax was tested along with obinutuzumab and compared with obinutuzumab plus chlorambucil in treatment-naïve CLL patients with co-morbidities. The 2-year PFS was significantly higher with venetoclax and obinutuzumab. This outcome was sustained in patients with a loss of TP53 function as well as unmutated immunoglobulin heavy-chain genes [67]. A global, phase 3, multicenter trial (ELEVATE TN) in patients with treatment-naïve CLL evaluated obinutuzumab–acalabrutinib, acalabrutinib monotherapy and an obinutuzumab–chlorambucil combination. The 2-year PFS was 93% with acalabrutinib–obinutuzumab, 87% with acalabrutinib monotherapy and 47% with obinutuzumab–chlorambucil. Adverse effects were lower with the acalabrutinib combination vs. the chlorambucil one. This trial proposed obinutuzumab/acalabrutinib as a front-line therapy for previously untreated CLL patients [15].

6. Mantle Cell Lymphoma (MCL)

RTX in combination with chemotherapy showed superior outcomes compared to chemotherapy in MCL. RTX was then evaluated with newer targeted inhibitors like BTKi and was found to have chemotherapy-sparing effects with no new major adverse events. Newer anti-CD20 antibodies like Ofatumumab in combination with chemotherapy have shown favorable outcomes in MCL but whether they outperform RTX or not needs further substantiation.

A retrospective database study showed that RTX improves the OS in older patients with MCL as part of an induction regimen with CHOP (or CHOP-like) chemotherapy [68]. A study investigated R-CHOP vs. R-FC in older patients with MCL. One of the conclusions from this study was that RTX maintenance therapy after R-CHOP induction showed a significantly prolonged OS [69]. RTX maintenance therapy was evaluated in MCL patients who underwent chemoimmunotherapy after ASCT. The 4-year PFS was 83% in the RTX group compared to 64% in the observation group ($p < 0.001$). After Cox regression analysis, the 4-year OS was higher in the RTX group than in the observation group (HR: 0.50; 95% CI, 0.26 to 0.99; $p = 0.04$) [70].

A single-arm phase 2 clinical trial evaluated a non-chemotherapy regimen with ibrutinib and rituximab (IR) in treatment-naïve older patients with MCL (age $\geq$ 65 years). The best overall response rate was 96%, with 71% achieving CR. The 3-year survival was 87% and 94%, in patients with low and moderate Ki-67%, respectively [71]. A phase 2 trial included treatment-naïve MCL patients and treated them with 12 cycles of IR and then, if they had CR, with 4 cycles of R-Hyper-CVAD (Hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) alternating with methotrexate and cytarabine (MT-C). If they did not achieve CR, they received two cycles of R-Hyper-CVAD alternating with MT-C, up to a total of eight cycles. The results showed that the IR combination had no concerning safety signals and led to a reduction in total chemotherapy, subsequently

attenuating chemotherapy-related side effects [72]. These studies showed that rituximab, along with newer targeted therapies, has the potential to improve efficacy outcomes for MCL patients with the added advantage of reduced adverse events.

A phase 2 study evaluated ofatumumab and ofatumumab plus bendamustine in transplant-ineligible MCL patients [73]. The ORR and mPFS with Ofatumumab monotherapy were 1/6 (17%) and 0.6 years, respectively, while with the Ofatumumab + bendamustine combination the ORR, mPFS and mOS were 23/25 (92%), 2.5 years and 7.4 years, respectively. It showed a favorable toxicity profile and similar efficacy to the RTX + bendamustine combination but failed to demonstrate superiority [73]. Another phase 2 study combined Ofatumumab with HyperCVAD for 4–6 cycles followed by high-dose methotrexate and cytarabine and autologous stem cell transplantation (ASCT) in 37 patients with newly diagnosed MCL. The ORR was 86% and CR was 73%. The mPFS and mOS were 45.5 months and 56 months, respectively. The MRD negativity rate was 96% at the end of induction [17]. This study hinted towards the higher efficacy of ofatumumab but necessitated further substantiation.

7. Other Investigational Anti CD-20 Antibodies

Veltuzumab is a humanized second-generation anti-CD20 monoclonal antibody. A multicenter phase 1/2 trial studied its safety, efficacy and immunogenicity in 82 patients with R/R B-cell NHL [74]. The overall ORR was 40.7% [74]. Veltuzumab was proven safe and efficacious at all tested doses and needs further studies to be compared with RTX and other anti-CD20 antibodies. Ocrelizumab is another humanized second-generation anti-CD20 monoclonal antibody. It was evaluated in 47 patients with R/R FL after prior RTX therapy [75]. The ORR was 38% and the mPFS at 28 months was 11.4 months. It was well tolerated, with grade 3/4 AEs occurring in <10% of the patients [75]. Ocaratuzumab is a third-generation humanized IgG1 anti-CD20 antibody. FcγRIIIa affinity is important for ADCC and those with phenylalanine instead of valine in position 158 have a reduced ability to mediate ADCC and clinically appear to have inferior outcomes after antibody therapy. One approach to improving efficacy is to enhance the ability of antibodies to mediate ADCC by lessening the biological impact of the FcγRIIIa genotype. A phase 2 study evaluated the safety and efficacy of Ocaratuzumab in 50 patients with previously treated FL and a low-affinity FcγRIIIa genotype [76]. The ORR was 30% and mPFS was 38.3 weeks [76]. Grade 3–5 AEs occurred in 13 patients [76].

Ublituximab is a type I chimeric, glycoengineered anti-CD20 monoclonal antibody. It was tested in RTX refractory patients with B-cell NHL or CLL [77]. The mPFS was 7.7 months for CLL patients [77]. Another phase 1 study showed promising results for Ublituximab in combination with Umbralisib and Ibrutinib in patients with CLL and NHL. A total of 37 (84%) of 44 patients achieved an ORR [78]. The authors concluded that the combination of Ublituximab, Umbralisib and ibrutinib was safe and had encouraging efficacy [78]. However, it would require further investigation.

EMAB-6 is another chimeric anti-CD20 monoclonal antibody. EMAB-6 induced a higher in vitro ADCC against CLL cells and higher FcγRIIIA-mediated interleukin-2 production by FcγRIIIA+ Jurkat cells in the presence of CLL cells at both low and maximally saturating concentrations [79]. The authors concluded that EMAB-6 represents a promising drug candidate for the treatment of CLL by inducing strong cytotoxicity against tumor cells that express low CD20 levels [79].

8. Rituximab Biosimilars

CT-P10 (Truxima) was the first biosimilar approved for rituximab. It was initially approved for NHL and then subsequently for CLL. A randomized controlled trial evaluated CT-P10 in combination with chemotherapy in advanced FL and demonstrated that it was non-inferior (97% overall response with CT-P10 vs. 92.6% with RTX) and pharmacokinetically similar to RTX. Treatment-related AEs were similar in both groups (83% in the CT-P10 group vs. 80% in the RTX group) [80]. Another study evaluated CT-P10 in low-burden

FL as a monotherapy vs. RTX. It showed that CT-P10 was similar in efficacy and had a comparable safety profile with RTX (5% with CT-P10 vs. 2% in RTX) [81]. PF-05280586 (Ruxience) is another RTX biosimilar that is approved for NHL and CLL. It was evaluated in low-burden FL and was noted to have an identical efficacy (ORR—75.5% in PF-05280586 arm vs. 70.7% in RTX arm) and safety profile [82]. ABP 798 (Riabni) was also approved as an RTX biosimilar. The JASMINE study evaluated it against RTX in grade 1-3a FL and found that the sensitivity analysis results were consistent with the primary endpoint for the risk difference (RD) of the ORR by week 28. ABP 798 was also comparable to RTX across secondary endpoints, which included safety [83]. Initially data were lacking regarding the interchangeability of RTX and its biosimilars. However, recent data showed that it may be safe to switch from RTX to a biosimilar product and vice versa. Furthermore, the incidence of allergic reactions is not significantly different [81–83]. Rixathon is another biosimilar that is still waiting for approval from the US FDA but has been approved by the European Medical Agency for NHL and CLL. A study from Jordan was recently published regarding the cost comparisons of rituximab biosimilars with reference to RTX Mabthera. It showed that for every JOD 1 spent on Rixathon, an extra JOD 3.21 needed to be spent on Mabthera. Rixathon had the lowest annual cost per patient followed by Truxima and Tromax, in comparison to reference Mabthera. In the US, the cost of the biosimilar Truxima is somewhat higher than Riabni and Ruxience [84]. However, Truxima is cheaper than the reference Rituxan [84]. RTX biosimilars have shown non-inferior efficacy and similar safety profiles and may be beneficial for patients, particularly those who come from underprivileged backgrounds.

9. Discussion

RTX became a significant therapeutic development in the armamentarium against most B-cell lymphomas. The addition of RTX to standard-of-care chemotherapy has led to improved outcomes in FL, DLBCL, MCL and other indolent NHLs in the front-line as well as in the R/R setting [3]. RTX maintenance therapy after induction with chemotherapy has also been shown to improve the PFS in FL [31]. In CLL, RTX plus chemotherapy has led to substantially higher PFS, OS and CR rates compared to chemotherapy [58]. With the advent of BTKi, like ibrutinib, and BCL2 inhibitors, like venetoclax, RTX is used in conjunction with them to facilitate better outcomes. The mechanisms of rituximab's refractoriness are not entirely clear. However, a significant proportion of patients with lymphomas, especially aggressive ones, attain resistance to rituximab [18]. Several newer anti-CD20 antibodies have been developed through biological modifications of the mAb Fc region. The intention of such modifications is to potentiate the effector functions of the Fc region including the ADCC, CDC and ADCP, which may subsequently result in accentuated anti-tumor action [8]. Several such anti-CD20 antibodies have been evaluated in clinical trials. Ofatumumab was developed such that it binds to a different epitope and leads to enhanced ADCC. However, the outcomes did not differ in comparison to rituximab in FL, DLBCL and other indolent NHL [37]. However, it has shown higher in vitro activity than RTX and was approved for CLL more than a decade ago in the R/R setting. However, with several other options in the therapeutic arsenal for CLL, its role as a monotherapy is undefined. It has also shown better in vitro activity in MCL but clinical data are pending. AEs including IRRs, infections, cardiovascular events and rash were higher with ofatumumab compared to RTX in FL trials. Furthermore, even in DLBCL trials, ofatumumab showed a higher incidence of rash and acute kidney injury compared to RTX. However, SAEs were similar in both treatment groups. Obinutuzumab is a third-generation anti-CD20 antibody that was designed such that it led to enhanced ADCC at the cost of a decreased CDC. It showed superiority over RTX in FL in the GALLUM trial and was approved for FL [5,16,43]. Notably, the incidence of Grade 3 to 5 AEs, particularly the incidence of infusion reactions, was significantly higher with obinutuzumab than with RTX [5]. AEs leading to the discontinuation of treatment were slightly higher by 2% in the obinutuzumab arm. Long-term follow-up studies also noted a slightly higher

incidence of adverse events in the obinutuzumab arm. Obinutuzumab failed to show superiority in DLBCL. It is also approved for the front-line treatment of CLL as it has demonstrated enhanced clinical activity but is most often used in conjunction with BTKi and venetoclax. It has shown stronger anti-MCL activity in pre-clinical models compared to rituximab, but clinical data is awaited. Rituximab still remains the anti-CD20 antibody of choice in conjunction with chemotherapy or newer targeted drugs for the treatment of B-cell lymphomas, due to its extensive safety data due to decades of usage and decreased costs due to the availability of generics and biosimilars. Furthermore, several newer agents have not been able to clearly establish superiority in several types of NHLs. They also bear a significant financial burden for patients and have increased AEs [3,16]. The cost of obinutuzumab is significantly higher than Rituxan [85]. In summary, despite the availability of multiple other anti-CD20 antibodies, RTX remains the standard-of-care anti-CD20 antibody for the treatment of B-cell lymphoma.

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