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Jacobs Journal of Cancer Science and Research

Review Article

Mechanisms of Resistance to Rituximab in B-cell Lymphoma

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Received: 02-26-2015

Accepted: 04-20-2015

Published: 04-22-2015

Abstract

Rituximab or Anti-CD20, is a chimeric monoclonal antibody (MoAb)that has become a ubiquitous component for improved therapeutic options for patients with B-cell non-Hodgkin lymphoma (B-NHL)and other known hematological malignancies. The MoAbs has the direct antiproliferative effect on the B cells in vitro. This review article focuses on the mechanism of resistance to the Rituximab(anti CD-20)mediated cytotoxicity.Understanding of the complexity of mechanism facilitates the progressof pharmacological strategies to reduce resistance.Unluckily, the common responses to single-agent Rituximab are inadequate, It has multiple mechanisms which commonly includes antibody-dependent cell- mediated cytotoxicity and complement-dependent cytotoxicity. Tumor/host -associated factors contribute to the Rituximab resistance. There are many approaches to overcome rituximab resistance such as engineered antibodies, radio-immunoconjugates and rational biologic combination immunotherapy, which provide a comprehensive understanding of interactions between its multiple mechanisms of action.Furthermore, few discussed studies in this review show that treatment with rituximab can be modified and may have a significant role in newer therapeutical strategies.

Keywords: B-cell non-Hodgkin Lymphoma (B-NHL); Antibody Dependent Cell Mediated Cytotoxicity (ADCC); Complement Dependent Cytotoxicity (CDC); Anti-CD20, Monoclonal-Antibody; B-cell depletion

Abbreviations

B-NHL- B-cell non-Hodgkin lymphoma
ADCC- antibody dependent cell mediated cytotoxicity
CDC - complement dependent cytotoxicity
USFDA- Food and Drug Administration U.S.
IgG- Immunoglobin G
DHL 4- lymphoma cells derived
RRCL- Rituximab-resistant cell lines
LRD- lipid raft domain
CHOP- Cyclophosphamide, Hydroxydaunorubicin, Oncovin(Vincristine) and Prednisone
Fc - Fragment, crystallizable region of antibody
DLBCL- Diffuse large B-cell lymphoma

Introduction

Based on the safety and efficacy data,rituximab, a chimeric monoclonal antibody was approved by USFDA on 26 November1997 for the treatment of non-Hodgkin lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), Rheumatoid Arthritis (RA) and Granulomatosis with Polyangiitis (GPA)(Wegener'sGranulomatosis) and Microscopic Polyangiitis (MPA) [1]. For NHL, rituximab can be used alone or in combination with other chemotherapy medicine.

It is the recombinant DNA technology made IgG1 kappa antibody targeting the CD20 antigen, which is usually found on malignant or normal B lymphocytes. It has molecular weight of approximately 145kD with binding affity of approximately 8.0 nM towards CD20 antigen. Antibody Isotype IgG1 (Immunoglobin G) contains light and heavy variable chain sequence. Rituximib is composed of 213 amino acids, in lightchain and 451 amino acids in the heavy chain [2]. It is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Non-Hodgkin lymphoma (NHL) is a cancer of the B lymphocytes. Bone marrow, spleen, thymus, adenoids and tonsils, digestive tract and lymph nodes are the major sites of lymphoid tissues which have more chances to develop lymphomas [3].

It is about 2-4 % of all malignancies [4]. Major symptoms of NHL include: Decrease in weight, sweating at night, chest pain, fever, fatigue, difficulty in breathing, swelling/pain in abdomen, and swelling in lymph nodes.NHL may include bulky mass in its advanced states Risk. The most common types of NHL are B and T-Cell lymphomas. About 85% of the NHL is B-cell lymphoma in the United States of America [5]. Rituximab was first developed by IDEC pharmaceutical and at present it is co-marketed by Genetech and Biogen Idec. It kills malignant B cells both circulating and tissue based b cells that have CD20 antigen on their surface; hence, it has a significant role in the treatment of NHL [6].

Epidemiology of Non-Hodgkin lymphoma and Hematological malignancies

Non-Hodgkin lymphoma (NHL) is a combined word for a various group of lymphoproliferative malignancies with differing patterns of responses and behavior of treatment. The majority (i.e. , 80-90%) of NHLs are of B-cell origin. Incidence of NHL is raising at 3% every year and reached more than 80% since 1973. Difference in incidence can be due to age, sex and race. The median age of all types of NHL is more than 50 years. In children, most commonly seen is high grade lymphoblastic and small non-cleaved cell lymphomas of B cells NHL. It is more common in male than female; and higher is white people than African American people [7].

Leukemia, plasma cell neoplasm and lymphoma are the most common heterogeneous hematological malignancies. In western countries the rate of incidence is increasing and seems very difficult to define its epidemiological behavior [8].

Table 1. Estimated new cases hematological cancers in 2005.

	Europe	EEA[a]	European Union	United States
	No. of cases	No. of cases	No. of cases	No. of cases
Lymphomas	121 200	104 600	101 400	63 740
Non-Hodgkin's lymphoma	ND[b]	64 400	62 300	56 390
Hodgkin's lymphoma	ND[b]	10 500	10 300	7350
Multiple myeloma	ND[b]	29 700	28 700	15 980
Leukemia	75 700	55 800	54 400	34 810

ND : Not Disclosed

[a]*EEA plus Switzerland:* 25 European Union countries plus Iceland, Liechtenstein, and Norway. *Europe:* EEA plus Albania, Belarus, Bosnia and Herzegovina, Bulgaria, Macedonia, Moldova, Romania, Russian Federation, Serbia and Montenegro, Switzerland, and Ukraine.EEA, European economic area; ND, not determined. [8].

Mechanism of action of Rituixmab

Rituximab is a monoclonal antibody that targets the CD20

antigen which expressed on the surface of pre and matures B lymphocytes. Once bind to the CD20, rituximab signals the B-cell lysis. The cell lysis mechanism is performed by antibody dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).

In ADCC, Fc gamma receptor binds on the Fc region of the antibody which is present on the surface of immune effector cells. These are nonspecific cytotoxic cells, such as macrophages, monocytes, eosionophils and natural killer cells. Frequency of ADCC is higher with IgG1 and IgG3 antibodies.

In CDC mechanism, the C1q binds the antibody region, which leads to the construction of the membrane attack complex [8]. Rituximab does not kill all malignant B cells and after prolonged exposure, existing B cells adopt resistance to the later rituximab therapy but in some cases expression of CD 20 still remain in the malignant B cells The survived resistant cells take the residence in the compartment, where they can be resistant to rituximab therapy but possibility of this mechanism is poorly known. After some period of time, several adaptative mechanism start initiating by which, target cells can escape from the rituximab-mediated cytotoxicity [9].

1.1. Structure and function of CD-20 and Rituximab

B- Lymphocytes antigen or CD 20 is a glycosylated phosphoprotein [10] encoded by MS4A1 gene (membrane-spanning 4A) [11] that codes a molecule receptor on the surface of B cell, which is responsible for differentiation and development of B cell [12]. Rituximab Fab, a crystal structure consists of CD 20 epitope with peptide, residual at 163-187. Combining site of the Fab region of this antibody forms a large pocket which puts up the epitope. Bounded peptide forms a unique cyclic circle by a disulphide bond with rigid proline residue at 172. 170, 173 motif of CD 20 is embedded into the pocket which helps in the binding of Rituximab. Hydrogen bond and Vander wall contacts, plays a role in antigen-antibody interaction. This site provides recognition of CD 20 with high affinity and specificity [13].

Rituximab binding with CD 20 is the main function in the treatment of hematological malignancies. It stimulates the Natural killer cells to activate antibody dependent cellular cytotoxicity (ADCC), but still it is less known about the interactions of cells during ADCC and how it stimulates ADCC when rituximab is given to patients. With the use of laser scanning confocal microscopy, it is possible to find that how CD 20 binds to the surface of B- cell. Other proteins like moesin and molecule 1 also play a role interaction between them. Rate of reaction of natural killer NK cells increases when they are polarized. Polarized B cell acts more frequently when it is capped with CD 20, resulting in interaction between target cell and immune cell. As a result, rituximab develops a polarization on B cells and it increases the therapeutic function for the purpose of NK –mediated ADCC [14].

1.2 Mechanism of Anti- CD 20 involved in the B-cell depletion

In late 1990s, advancement has been seen in the treatment of lymphopoliferative disorders which offers medical practitioners to effectively target the B-cell compartment. CD-20 is a Ca-permeable channel whose effects are restricted to the pre-B cell to the immunoblast stage. A single course of rituximab does diminish peripheral human B lymphocytes for about 3 months to more than one year involving Fc , apoptosis and complement dependent killing of target cells as shown in figure 1.

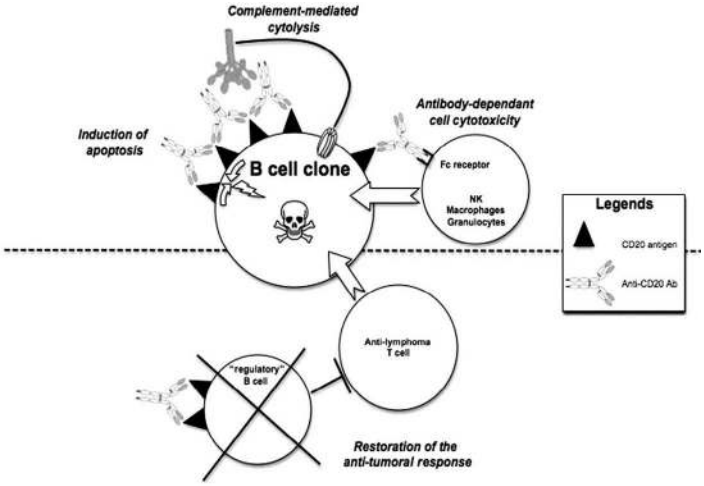

Figure 1. Apoptosis of malignant B cell clones happens upon cross-linking Rituximab-CD 20 complexes in the lipid rafts, and it activates cell signaling way, including Src Kinase and their regulatory molecules.CDC helps in the inability of anti-CD20 IgG1 along with C1 and the trigger, ADCC mechanism requires an interlinked Fc portion and rituximab and receptor on target cells[16].

Many studies have focused on circulatory dynamics and micro-environment for the efficacy of rituximab which reduced the number of B –cells. Death of malignant B cells occurs upon rituximab and CD 20 cross linked complexes in the lipid raft, as a result of apoptosis of B cells , signaling pathway gets start activating involving Src Kinase and regulatory molecules. Classical complement pathway may be activated once anti CD-20 immunoglobulin G1 gets attached to their antigen for the purpose of binding C1.ADCC mechanism requires the boundage between Fc portion of rituximab and selective recptors which present on effector cells. Lysis of malignant B cells could be possible by restoration of the protective antitumoralresponse . If distruction of any non malignantcells occurs then immune regulatory properties facilitate the production of new antitumoral clones of T cells [15].

Tumor associated and host associated resistance is very com-

mon while treating patients with hematological malignancies [16]. Multiple mechanisms are involved on a cellular and molecular level to relieve from immune mediated rejection [17]. Action of ADCC mechanism have shown major effector role. Some of the rare cases reports loss of CD 20 antigen along the resistance building process. An increase of complement resistant protein hasbeenseen, but the reason for loss of sensitivity is not clear.Therefore, combination therapy can give the better presentation for the augmenting antibody based killing [18]. Involvement of global CD20 gene and protein at per and post phase of transcription would result in rituximab resistance in lymphoma cell lines.

1.3 Mechanism of action of Rituximab on target cell

Rituximab stimulates the lysis process of B-cell after binding with CD 20 through CDC and ADCC. RTX helps in the apoptosis of DHL 4, human B cell lymphoma cell line (DHL derived from the acute phase of human follicular B cell lymphoma) [19]. B-cells may act on multiple site of inflammatory process in NHL patients, which result in depletion of circulating and tissue-based B cells [19]. In recent days, statistics have shown that major effective management is ADCC with a minor role of complement. After treatment, resistance to rituximab can be developed. The molecular pathogenesis is still little known and CD 20 antigen could be lost [20].

1.4 Effect of rituximab in children with malignant hematological disorders

Rituximab has been extensively used in adult patients. Rituximab is investigated in including autoimmune hemolytic anemia (AIHA) [21]. antibodies to factor VIII and IX chronic immune thrombocytopenic purpura [22] and post transplant B-NHL [23]. Studies show that first line of treatment with rituximab; especially, in AIHA, and PTLD in the pediatric population is deemed to be safe and effective [24].

2. Pharmacodynamics of rituximab

Tran et al, in 2010 studied the pharmacokinetics characteristic of the rituximab in the CD 20+ positive B cell malignancies. First course of the treatment had started with combination therapy of chemotherapy along and with rituximab for four to eight cycles, followed with the maintenance dose for up to year (2 or 3 monthly dosage of 375 mg/m2) and after that it was given to the patients for 2 years of 2 or 3 monthly dosage of 375 mg/m2 rituximab. Blood sample was collected in pre and post treatment for the measurement of rituximab with ELISA (enzyme –linked immunosorbent assay) and also performed antigen binding assay for human-antibodies against chimeric-antibodies except one patient with CLL, rest of 7 patients showed complete response in first series of the treatment. In 4 patients rituximab level was constant ***in the*** maintenance therapy phase with an average of 6 mu g/mL concentration. Estimated half life was measured 19.2 days.

Pharmacokinetic-pharmacodynamics: Relationship of rituximab level was measured low in non responder as opposed to the responders. Incomparision to responder patients.

Noted: The total number of patients were deemed to be result was evaluated for small. Therefore the claims may be further investigated number of people so, it should be subject of more research [25].

2.1 Methodology of resistance to Rituximab in B-cell lymphoma

In spite of significant clinical outcomes with the use of rituximab, some patients with B- non-Hodgkin's lymphoma develop resistance to it. A study has been performed in which three cell lines ((Raji, RL, and SUDHL-4) of rituximab resistant B cell have analyzed. RSCL (rituximab sensitive cell lines), Raji, Rl, and SUDHL-4 along with RRCL were exposed to different concentrations by different chemotherapeutic agents; and measurements of apoptotic cell were also performed. It was observed that RRCL was found resistant and its expression was decreased [26].

Human originated rituximab has a heavy chain that allows to link with Fc receptor for IgG of the host cell. In ADCC mechanism, there are three kinds of Fc receptors (FcγRI, FcγRII, and FcγRIII) present on antibody which has the ability to induce ADCC. Once this process is activated, effecter cells are able to induce ADCC towards the target cell. ADCC is also known for major anti- tumor mechanism, and its interaction is important to induce it. Responses of Rituximab depends on the FCγRIIIa receptor, and amino acids positioned 158 of the protein determine the functionality of ADCC [27].

The complement-dependent cytotoxic (CDC) is a curative mechanism which helps in the treatment of CLL (chronic lymphocytic leukemia) [28]. Activity of the CDC is stimulated by some antibodies when binds with the surface of target cell. Some molecules with immunomodulative efficiency activates the complement system such as formation of MAC (membrane attack complex) from glycan and production of C3a, C4a, C5a (pro-inflammetry molecules) responsible for stimulating various effectors (e.g. monocytes, Nk cells and macrophages) for the lysis of target cell [29].

2.2 Occurrence of rituximab resistance in lymphoma cell lines is related to both CD20 gene and protein down-regulation regulated at the transcriptional phase

Myron and his associates developed rituximab resistance cell lines (RRCL) and studied changes in the expression and structure of CD 20, LRD (lipid raft domain) reorganization , ADCC, CDC, calcium mobilization between parental and rituximab re-

sistant cell lines [30]. Cell lines of rituximab-resistant (RRCL) and rituximab-sensitive (RSCL) is established. In RRCL significant reduction have seen in rituximab mediated ADCC and CMC while performing RRCL.Phenotypic changes also have been seen on the surface of CD 20 antigen.Consequential Calcium mobilization results have come once it is exposed under in vitro condition with rituximabin lymphoma cell lines.It has been assumed that CD 20 serves as a calcium channel directly. In addition , a 35kDa protein band also have found in the RRCL, which was not present in the parental cell.Due to developed resistance , it also changes expression of CD 20 antigen in RRCL. A proteasome inhibitor PS-341 increases the expression of CD 20 under *in vitro* condition and partial improvement have seen to the rituximab associated CMC at the pre and post transcriptional phases. Statistical data reports the resistance of rituximab and down regulation of CD 20, which have been seen while chronic exposure of B cell lymphoma is indicated. Proteasome inhibitors showed the path of future additional mediators and complementary drugs/biological agents to overcome the resistance against RRCL [30].

2.3 Review of use of rituximab for the treatment of chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL)

Plosker and Figgittin 2003 conducted two pivotal trials and found that the rituximab has significant efficacay associated with B-cell malignancies.Rituximab is used as a viable option in case of relapsed or refractory indolent NHL and as a standard first line treatment option was used when given with cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy (CHOP) in patients with diffuse large B cell lymphoma. Patients who receivced intravenous administration of 375 mg/m(2) of rituximab once weekly for four weeks have shown a similar result as opposed to the "chemotherapy ."CHOP plus rituximab and CHOP alone in elderly patients with diffuse large B –cell lymphoma has shown that combination treatement of CHOP and rituximab significantly; with higher effect and less adverse effects, as opposed to the alternative treatments.Rituximab could show better results specially in elder patients [31].

2.4 Regulation of Human Tumor B cells enhances the functionality of CD 20 through ERK-Dependent Mechanism

Rituximab has shown good results in the apoptosis of the targeted cell in response to against CD 20. In some patients , low expression of CD 20 have been observed once patients is administrated with rituximab.The role of CD 20 is not entirely known at this time. Therefore, the mechanism of depletion and built resistance is not definitely appreciated [32]. Wojciechowski and his associates investigated the effect of bryostatin-1 which is an immune modulator and having antitumor activity. It is considered to beused for the detection of the expression of CD 20 in NHL cells through ERK ½ pathway.Bryostatin 1 enhances the expression of CD 20 mRNA. This was done by by MAPK kinase and ERK signal transduction pathway. As a result it was concluded that combination of rituximab and bryostatin could become a valuable combination therapy option for the NHL patients [32].

3. Overcome BTZ resistance

3.1 Anti CD20 or rituximab mediated CDC and epoxyketone-based irreversible proteasome inhibitors which helps to overcome BTZ resistannce

Verbrugge and others in 2013, investigated the molecular basis of developed resistance to bortezomib in JY cell line in B lymphoblastic cells. Efficiency of rituximab treatment have become the cornerstone in B cell malignancies. Furthermore, a number of patients are either resistant or show a limited response. Molecular basis of resistance depends on the expression of CD 20. Thus, new therapeutic modalities such as bortezomib (BTZ) and proteasome inhibitors (PIs) are needed. Patients with resistant to rituximab present significant apoptosis of tumor cells after administration of BTZ.Rapid BTZ induced apoptosis even in rituximab resistant patients are observed. Proficient B cell targeting by proteosome inhibitors are dependant upon secretion of proteins and their substantial turnover which are important for rendering these cells and leads to the interference in protein homeostatis and inhibition of UPS ubiquitin proteasome system:A master regulator which controls the apoptosis induction and induces the pro inflammatory cytokines. Thus, along with rituximab and BTZ & PI an effective role in the depletion of B cells malignencies and autoimmune disease are considered [33].

3.2 Phase II clinical trial of Oral administration of rituximab and lenalidomide in patients with follicular, refractory diffuse cells and transformed lymphoma

Combination therapy of rituximab and lenalidomide is effective in follicular 1-2 grade and mantle cell lymphoma, but still unknown in grade3 follicular lymphoma (FLG3) , diffuse large B cell lymphoma (DLBL) and transformed large cell lymphoma (TL) . Fourty five (45) patients with DLBL , FLG3 and TL had received 20 mg lenalidomide orally for 28 days and also given rituximab 375 mg/m2 intravenously weekly in cycle one (how many cycles were given). Grade 3-4 toxicities included neutropenia, thrombocytopenia , anemia and leucopenia were deemed to be related to the treatment. The Overall Response Rate (ORR) was 33 % over 10.2 months.Rituximab plus oral lenalidomidewere considered to be well tolerated in patients with refactory/relapsed TL and DLBCL [34].

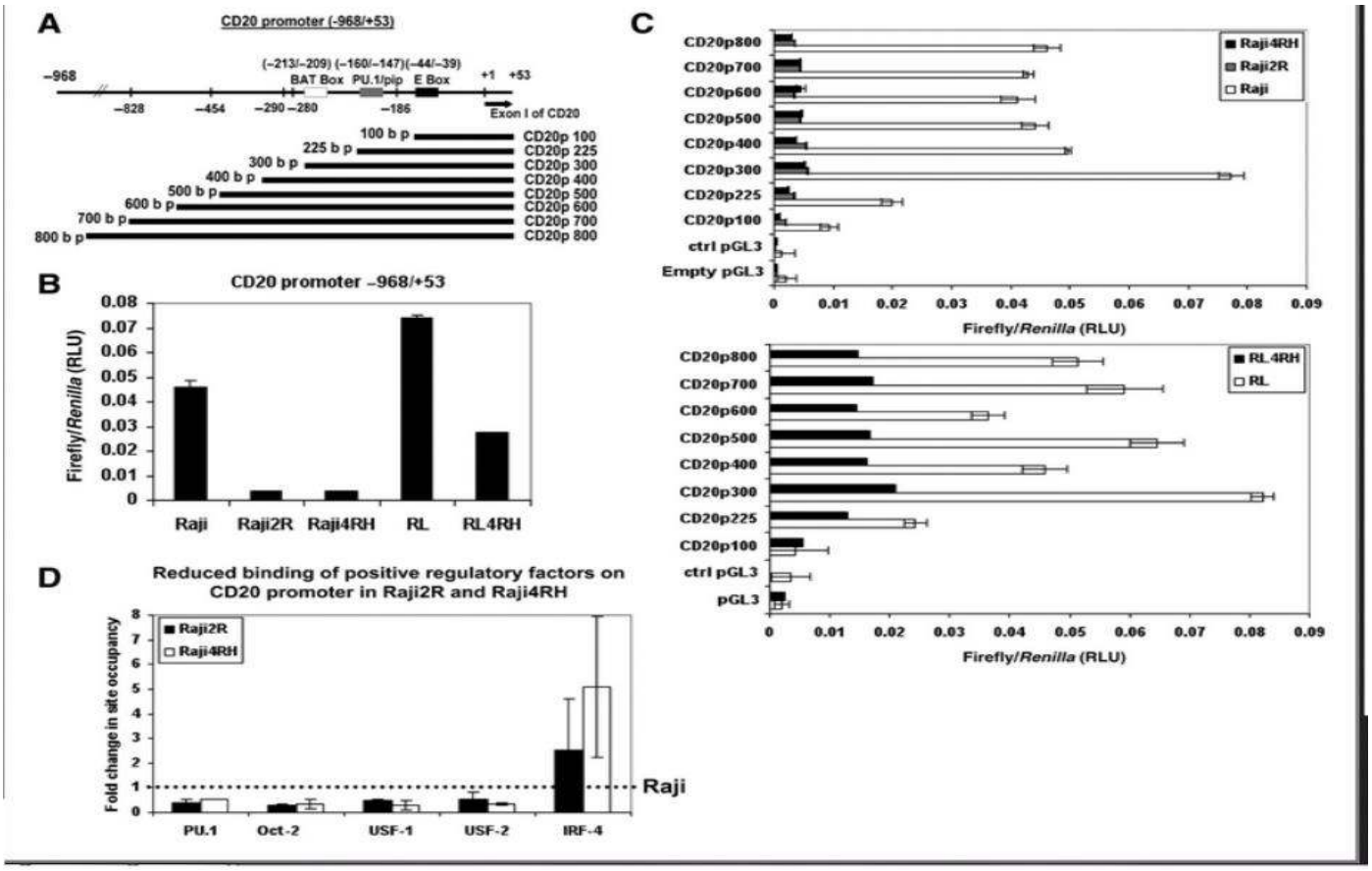

Figure 2. Reduction in CD 20 promoter in the RRCL [24].

3.3 Mode of regulation of CD 20 for B-NHL in rituximan resistant cell lines

The contribution of antigen present on CD 20 which is responsible for rituximab-resistant cell lines (RRCL) was investigated by Tsai et al (2012). Multiple mechanisms such as CD 20 knockdown, analysis of CD20 promoter, CD20 plasmid transfection chromium-51 release assays, immunohistochemical staining, flow cytometric analysis and chromatin immune precipitation to define CD 20 regulation in RRCL were considered. Gradual loss of CD 20 surface had been identified, and a correlation between rituximab-CMC (complement-mediated cytotoxicity) and CD 20 surface expression was observed. Analysis of CD 20 in RRCL showed reduced binding of various key positive regulatory protein on CD 20 while in RRCL. Several mechanism were proposed to be responsible for altering the expression of CD 20 in RRCLas shown in Figure 2 [35].

Rituximab efficiency depends on tumor and host related factors.Variations in the individual accessory mechanism such as ADCC and/or CDC may influence the activity of rituximab. Alteration in CD 20, regulation in signaling and mitochondrial pathyway, and variations in lipid raft domain are considered as a part of tumor related factors.The increased rate in the alteration of CD 20 antigens increases the chance of resistance to rituximab [36].

3.4 Safety and efficacy of re-treatment with Rituximab

A phase II trial investigated the safety and efficacy of rituximab in relapsed patients with follicular NHL with previous treatment of rituximab.A total of 58 patients were enrolled. .All 56 patients took all four scheduled dosages. Two paients reveived a single infusion .Most of the adverse events such as transient fever , chills, pruritus and asthenia were observed during the treatment period. No deaths were reported. Cases of the reported infections were reported as mild. The overall response rate was roughly 40%,. There were of CR and 30% of PR. In short, multiple courses of rituximab is deemed as safe and effective in this population [37].

3.5 Role of Cross resistance and altered cell signaling in the development of rituximab resistant lymphoma clones.

Either in combination or as a single agent , rituximab has demonstrated significantly positive results in lymphoma patients. Some patients have become unresponsive and resistant over time. To understand the methodology of resistant eventsin established Rituximab-Resistant (RR) clones,lym-

phoma line were compared with parental lines [38].Clones have had reduced surface CD 20 expression and did not show any responses like CDC or rituximab growth reduction. Rituximab was not able to chemosensitize the rituximab resistant clones, which had hyperactivation on the nuclear factor kB and extracellular signal regulated kinase ½ pathways. It lead to the overexpression of Bcl-2, higher drug resistance and myleiod cell differentiations. Additionally, it did not inhibit the pathway's activity and resistant factor. Therefore,continuous exposure ofrituximab in RR clones, have altered cell signaling system resulting indifferent types of genetic and phenotype properties compared to parental cells.

Noted: RR clones have "resistance" relation with rituximab and can be used with other agents such as, PD098059, bortezomib, and dehydroxymethylepoxyquinomicin [38].

4. Future Direction and development of Rituximab treatment

Rituximab is deemed as a revolutionary treatment option in the patients with B cell malignancies. It has has low response rate in CLL patients. Apart from its commonly known related adverse events including rapid tumor lysis and cytokine release syndrome, it is widely accepted for the treatment of NHL and other autoimmune diseases. Combination therapy along with the CHOP (cyclophosphamide, adriamycin, vincristine, predinisone) has changed the sceneriao of the treatment options [39]. Standard dose of rituximab (weekly x4) is well tolerated among patients with B malignancies. Additional investigations associated with the effective dose regiments as well as its benefits in combination therapy to avoid furtherresistance may be required [40].

4.1 Proposed biosimilar Rituximab, GP 2013

Biosimilar products are developed with the hope to toenhance the biological treatment and provide feasibility for patients with moretreatmentoptions.Mediated therapy associated with monoclonal antibodies could be deemed as both beneficial and affordable. GP2013 is deemed tobe the biosimilar product for Rituxan[41]. Physiochemical and functionality was compared with rituximab. X-ray crystallography, hydrogen deuterium exchange mass spectrometry (HDX-MS), DSC measurements, surface plasmon resonance (SPR), HPLC, and Bioassay were performed. Heavy and light chain of GP2013 expected same mass index as original rituximab. Sequence of amino acid and high order structures were all similar. Using a comprehensive methods of bioanalysis of GP2013 is very much similar to originat or rituximab [41].It is assumed that, bringing biosimilar of rituximab in market may cost around $10 to 40 million, and duration can be six to nine years which is more in comparision of generic. In Latin America, regulation of biosimilar products are yet to introduce and moving forward to increase the standard for these products. Rituximab is expected to expire in Dec, 2015 in the US [42].

Conclusion

Rituximab is a monoclonal antibody, widely used in various types of lymphomas and immunological disease. Rituximab's mechanism of actions includes: Direct apoptotic signaling, ADCC and CDC. But, its resistance remains as a challenge to manage B cell lymphoma.It is debatable whether the CD 20 expression is a major problem for resistant or not.A clear picture of its multiple mechanisms of actions are needed to better clarify the phenomenon of its resistance. Conjugation with other cytotoxic drugs may improve the clinical outcomes.

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