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Rituximab: A Hope for Lymphoma Patients

Ahmed M. Kabel[1,2,*], Ashwaq M. Al-Asmari[3], Maha J. Al-Gamdi[3], Rahaf S. Al-Qurashi[3], Abeer A. Al-Shehri[3], Arwa M. Al-Sudani[3]

[1]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, KSA
[2]Department of Pharmacology, Faculty of Medicine, Tanta University, Tanta, Egypt
[3]Fifth year student, College of Pharmacy, Taif University, Taif, KSA
*Corresponding author: drakabel@gmail.com

Abstract Rituximab is an antibody targeting the CD20 receptor protein of B-cells, the immune cell responsible for specific adaptive immune system properties. In B-cell lymphomas, where the B-cell lymphatic cells underlie the lymphoma phenotype, the use of rituximab to specifically target and destroy B-cells is a relatively recent strategy for treating lymphomas. Indeed, even recently it has been determined that classic Hodgkin's lymphoma can be treated by a special regimen of rituximab. Rituximab had such a pronounced effect on the survival rates of certain lymphomas that the survival outcomes have fundamentally changed. These outcomes have changed to the degree that prognostic tools used to infer survival rates have had to be overhauled. The exact molecular mechanisms of rituximab activity had recently been elucidated, and although heterogeneity in lymphoma response to rituximab exists, detailed molecular studies investigating this have as a result uncovered new molecular targets, such as CD55 and CD59. The above mentioned topics, as well as the toxicity of rituximab, the use of rituximab with supplemental treatments in parallel such as histone deacetylase inhibitors, radiation therapy, and the effects of rituximab on different types of lymphomas, are all reviewed here.

Keywords: *rituximab, lymphoma, patients*

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1. Introduction

Cancer is a group of diseases characterized by unregulated cell growth and differentiation [1]. Malignancies in the lymphatic system are manifested in the cells of that system, with several subtypes existing therein. In particular, there is a distinguishing between Hodgkin's lymphoma and the others (non-Hodgkin's). The difference lies in the type of immune cell endogenous to lymphatic system, which is the source of malignancy. Specifically, a lymphocyte is cancerous in Hodgkin's lymphoma, while other types are other cells native to the lymphatic system [2]. This includes B-cells, which are a type of immune cells responsible for adaptive immunity. When these lymphatic cells are cancerous, it constitutes B-cell lymphoma. Diffuse large B-cell lymphoma (DLBCL) is a non-Hodgkin's lymphoma, and is the most common subtype [3].

Rituximab is an antibody that targets specifically the CD20 protein receptor of B-cells, and ultimately destroys the B-cells [4]. In types of lymphoma, such as diffuse large B-cell lymphoma (DLBCL), this drug can be used to target and destroy B-cells, as well as in other diseases that are physiologically based on B-cells that are either over-reactive or dysfunctional in some ways [5]. Some of these diseases are characterized by an excessive number of B-cells or their activity, such as in autoimmune diseases. The antibody targets and binds to CD20 receptors which are suspected to play a role in calcium ion equilibrium in B-cells [6]. When the antibody binds to these proteins, the antibody changes the configuration of the B-cell, resulting in a promotion of natural killer (NK) cells killing the B-cell [7].

DLBCL is targeted with rituximab, but due to the heterogeneity of the disease, it has been found that rituximab must be supplemented with other chemotherapy regimens, in standard fashion. These chemotherapeutic supplements include cyclophosphamide, doxorubicin, vincristine and others, altogether increasing survival rates [8]. In a study examining the effects of rituximab introduction into general medical practice, 277 adult patients with de novo DLBCL were assessed. They found that the progression-free survival (PFS) increased after rituximab had been introduced to the population. There was a marked increase in PFS for the older group than the younger group. Also, they showed that those with high or high-intermediate risk showed less improvement in PFS score [3]. The aim of this minireview was to throw light on the potential mechanisms of action of rituximab and its role in management of various types of lymphoma.

2. Rituximab and Supplemental Treatments

2.1. Rituximab and Radiation Therapy

The utility of radiation therapy (RT) in combination with rituximab is an ongoing area of investigation. In a study, 4.5 years after treatment with RT and rituximab

over 800 patients were characterized for their potential interactions [9]. Researchers found that although rituximab is the new care standard for DLBCL across many jurisdictions, the benefit of RT was not accurately represented since the study identified that rituximab did not eliminate the tumor outcome measures. Given this, the authors found that a comparison of those who received RT did not have an overall positive benefit across all the statistical measures that they used.

2.2. HDAC and Rituximab

B-cell lymphoid malignancies were demonstrated to respond to the activity of histone deacetylase (HDAC) inhibitors, where HDAC is an enzyme responsible for modifying the epigenetic code of acetylation [10]. There was an evidence that the combination of rituximab and vorinostat, which is one of HDAC inhibitors, are capable of inciting synergistic responses in patients with B lymphoid malignancies. The explanation for the pathway targeted by vorinostat is not specific, but it may act as a generalized proinflammatory cytokine targeting protein [11]. It was suggested as well that other targets such as MYC protein are involved in the synergistic response of rituximab with vorinostat, although there are many agents in contemporary treatment programs that outperformed this combination, such as Lenalidomide, and Bortezomib [3].

3. Rituximab and Different Types of Lymphomas

3.1. Effects of Rituximab on Follicular and Mantle Cell Lymphomas

Follicular (FL) and mantle cell lymphomas (MCL) are diseases that have only recently been made treatable through a variety of treatment regimes, with palliative care being an option for the most severe disease phenotypes and manifestations [12]. Rituximab is one such treatment for FL and MCL, showing little toxicity and a remission frequency that is in line with much more complex combinatorial treatments. It was found that for FL patients, rituximab is a suitable option, especially in those cases where blood counts and tumor loads are minimal. The lack of added toxicity to a statistical degree even over a long treatment schedule demonstrates the suitability of rituximab as a treatment for FL as well as MCL diseases [13].

3.2. Rituximab in Hodgkin Lymphoma

Since the rituximab antibody targets and therefore depends on the presence of the CD20 receptor, any heterogeneity of cell-types can result in less than optimal targeting outcome [14]. However, in classical Hodgkin lymphoma (CHL) cells that express CD19 markers, the ability of rituximab to target CHL is bolstered in combination with ABVD chemotherapeutic supplement (includes doxorubicin, bleomycin, vinblastine, dacarbazine). Indeed, clinical outcomes suggest that CHL remission rates in the long term decrease with the addition of rituximab and ABVD, with 81% of patients showing remission in this study [15].

4. Rituximab and Survival Rates

The survival rates for diffuse large B-cell lymphoma (DLBCL) patients in all risk groups have seen major improvements since the introduction of rituximab to chemotherapy treatment [16]. The role of rituximab has expanded to improve the prognosis of both the indolent and aggressive lymphomas [17]. It was reported that the addition of rituximab to standard chemotherapy regimens improves the response rates and the survival outcomes in patients with follicular non-Hodgkin lymphoma (NHL) and DLBCL, the two most common subtypes of NHL. Population-based studies have proven substantial improvements in NHL survival over the past decade and indicated that rituximab has altered the long-term prognosis of follicular NHL and DLBCL patients [18].

5. Rituximab and CD20

5.1. Molecular Basis of Rituximab Activity

The molecular basis of action of rituximab has largely to do with the target of its activity: the CD20 surface receptor. The protein itself contains two known protein domains found in antibodies, the human IgG1 fused with the kappa constant domain [19]. Phase II trials have shown that the 50% response rate is due to patient heterogeneity, although the exact cause of this variation is unknown. What has been ruled out is that the localization or uniformity of the CD20 protein receptor is responsible, since the CD20 receptor is in fact expressed at high levels in those patients who are non-responsive to rituximab [20]. The mechanism of action of the rituximab antibody is not fully resolved, but likely involves cytotoxicity of the complement-mediated or antibody-dependent variety, yet closely related antibodies with highly similar protein structures to rituximab display different biological activity [19]. CD20 itself is 33-37 kiloDaltons (kd) in mass, which forms tetramers that together function as calcium ion channels, and is phosphorylated in both normal and abnormal B cells [21].

5.2. Impact of Rituximab on Lymphoma Cells

In Golay et al. [20], the biologic impact of rituximab on normal and abnormal B cells was tested in vitro. They investigated five different human lymphoma cell lines, one of which was Burkitt lymphoma, four were follicular lymphoma sub-types, three were fresh cases of follicular lymphoma, and normal B lymphocytes were assessed as a normal control. The authors examined the effects of rituximab on different B cell functional characteristics: proliferation, activation, apoptosis, antibody-dependent cell mediated cytotoxicity (ADCC), and complement-mediated cytotoxicity (CDC). The authors tested these functional properties by assessing B cell response to various infections done in vitro, after the B cells were exposed to rituximab. The first of these was in response to bacteria, which was inhibited successfully, but others were not. The authors conclude that CD55 and CD59 are important molecular factors in addition to CD20 required to explain the molecular mechanism of rituximab biological action. Lee et al. [22] reported that the addition of rituximab to CHOP (Cyclophosphamide, doxorubicin,

vincristine and prednisone) had a significant cytotoxic effect on lymphoma cells which improves the survival rate in patients with DLBCL and produces early survival benefit for very elderly patients, without any significant increase in the risk of adverse effects.

6. Molecular Markers of Rituximab Success

The use of both the prognostic index for risk prediction, as well as molecular markers, are together powerful tools for clinical prognosis of rituximab success rates in DLBCL patients [3]. Two promising and widely used molecular markers are the BCL2 and MYC transcripts, as well as their protein products [23]. There is controversy over the applicability of these markers to DLBCL treatments, with some studies being showcased as proof that the BCL2 marker inaccurately predicts the advantage of rituximab therapy, while others demonstrate the utility of BCL2 expression and problems therein as a reliable indicator of worsening patient outcomes [24]. By comparison, MYC mutations are predictors for decreased DLBCL survival outcomes, yet it has poor ability to mark rituximab suitability in isolation from BCL2 information [25].

Perry et al. [24] measured the expression of MYC and BCL2 using immunohistochemistry in the cells from DLBCL patients treated with rituximab. They evaluated 106 de novo cases of DLBCL that had been treated in those patients with the use of rituximab in conjunction with other chemotherapy drugs. The authors found, using multivariate statistics,that if MYC and BCL2 are both highly co-expressed, then this biomarker serves as a reliable predictor of poor survival in rituximab treated DLBCL patients; those with high MYC and BCL2 expression were nine times more likely to die from DLBCL. By contrast, those patients with low expression of either BCL2, or MYC, had the best prognosis, indicating that BCL2 and MYC are in some way functionally and/or causally responsible for the disease phenotype in DLBCL, and/or are effected in some way by the addition of rituximab in the therapeutic regimen. The authors argue that the cheap reliable techniques utilized to characterize these markers in vitro makes MYC and BCL2 advantageous for DLBCL prognosis. The use of these markers can be incorporated into prognostic tools as another way to separate DLBCL patients into risk groups rooted in molecular biology [26].

7. Conclusion

Rituximab had been shown to greatly increase the chance of success in treatment of lymphomas, both classical Hodgkin's as well as non-Hodgkin. The necessary revision of prognostic indices is evidence of the dramatic change in survival outcomes that the drug had on lymphoma suffering patients. Although the suitability of rituximab to other types of lymphomas still remains to be investigated, the ability for the drug to be combined with chemotherapy and radiotherapy in a synergistic fashion has broadened the potential therapeutic applications of rituximab.

Conflict of Interest

The authors declare that there is no conflict of interest.

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