

Progress in the Treatment of Hematological Diseases with Rituximab

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Abstract

Rituximab is a mouse and human chimeric CD₂₀ (anti-B cell) specific monoclonal antibody that has been approved by the U.S. Food and Drug Administration for the treatment of lymphoma. The expression of CD₂₀ antigen is expressed in the whole ontogeny of B cells, starting from the premature B cells in bone marrow to the differentiation of plasma cells in secondary lymphoid tissues. The wide distribution of CD₂₀ molecules allows rituximab to eliminate a large number of B cells. Rituximab is the core drug for the treatment of hematological diseases, often combined with drugs as a first-line treatment. Long-term hormone therapy often results in serious adverse reactions, and new therapies, which can avoid widespread immunotoxicity, have great potential for treating diseases of the blood system.

Keywords

Rituximab, Malignant Lymphoma, Leukemia, Multiple Myeloma, Autoimmune Diseases, Hematopoietic Stem Cell Transplantation

1. Introduction

Rituximab, a genetically engineered chimeric mouse/human IgG1- κ -anti-CD₂₀ monoclonal antibody (mAb), has been approved by the U.S. Food and Drug Administration for the treatment of various subtypes of B-cell non-Hodgkin's lymphoma (NHL). Clinical studies have demonstrated the efficacy of rituximab in the treatment of autoimmune diseases, such as rheumatoid arthritis [1] [2] and immune thrombocytopenic purpura (ITP), etc. [3]. Morath C *et al.* treated refractory thrombocytopenia and allogeneic SCT with rituximab in oral and ocular manifestations of cGVHD, and found that in addition to improved platelet count, cGVHD symptoms were also reduced and immunosuppression was

successfully stopped [4]. Subsequent small case series have shown mixed results of steroid-resistant cGVHD [5]-[11]. Thus, the induction of new mechanisms of cGVHD, including high activation and aberration of donor B cells, paves the way for new therapeutic modalities that ultimately improve allogeneic HSCT outcomes. In recent years, with the deepening understanding of B lymphocytes and their mechanism of action, the therapeutic scope of rituximab has expanded from B cell malignant lymphoma to chronic lymphocytic leukemia, multiple myeloma and a variety of autoimmune system diseases, and even plays an important role in hematopoietic stem cell transplantation. Rituximab rapidly clears B cells through cytotoxic action, which interferes or even inhibits the generation of autoimmune antibodies. It is effective in treating refractory AIHA in children [12]. Rituximab was well tolerated with fewer side effects. The main side effects include: 1) acute infusion reaction: hypotension, fever, chills, chills, bronchospasm, etc. which generally appear in the first application, can gradually reduce later. 2) The incidence of serological reaction is higher in infants [13]. 3) Long-term reduction in autoantibody production can increase the risk of viral and bacterial infections. Chickenpox virus [14], enterovirus [15], and pneumocystis carinii have been found. Therefore, serum immunoglobulin levels should be monitored and prophylactic gamma globulin infusion should be given during treatment, and treatment should be given to prevent pneumocystis carinii. The progress of its clinical application is as follows.

2. Rituximab in the Treatment of Chronic Lymphocytic Leukemia (CLL)

Chronic lymphoblastic leukemia (CLL) is the most common leukemia in Europe and the United States [16]. The incidence in China is significantly lower than that in western countries, but it is not rare. CLL can be identified from most other lymphatic proliferation and sputum diseases of the Bin area mainly according to typical lymphocyte morphology and immunophenotype characteristics, and some patients need to be identified by combining pathology, immunohistochemistry and cytogenetics. CLL weakly expressed CD20 was detected by flow cytometry, and standard dose rituximab was used to treat recurrent CLL. The total effective rate is 10 to 15 percent, and since. The duration of effect is shorter. Recent studies have shown that the expression level of CD20 does not affect the effective rate of treatment [17]. However, the increase of free CD20 antigen in the blood circulation of CLL patients makes rituximab neutralized before reaching target cells, so the serum rituximab concentration decreases, which is related to the short effective duration of rituximab [18]. In order to improve the efficacy of rituximab, a recent clinical trial increased the dose to 2250 mg/m² once a week for 4 times, with an overall response rate of up to 75%. The treaty-related toxicity was similar to the standard weekly use of rituximab, and the median effective remission time was 9.5 months. Another way to improve the efficacy of rituximab is through combination chemotherapy. Michael *et al.* [19]

reported a clinical study on the treatment of 224 newly treated advanced CLL patients with rituximab combined with fludarabine and cyclophosphamide (FC), and the results showed that the total effective rate was 95%. Some patients who had relapsed or failed after previous fludarabine or alkylating agent treatment were still effective after receiving rituximab combined with FC regimen again [20].

Rituximab is a chimeric antibody that binds to CD₂₀ antigen on the surface of B cells. Although it is highly effective for follicular lymphoma with an OR rate of 60%, the single drug rituximab has poor clinical activity against B-cell CLL, which is less effective in clearing the disease from bone marrow and has a short reaction period [21] [22]. The response rate of rituximab monotherapy in previously treated CLL patients was 23% - 45% (CR 0% - 3%) [21] [22]. Phase 2 studies demonstrated a dose-response correlation, and the response rate increased with the increase of rituximab dose [21]. The response rate at the dose of 500 - 825 mg/m² was 22% (all PR), and the response rates at the dose of 1000 - 1500 mg/m² and the highest dose of 2250 mg/m² were increased to 43% and 75% (P = 0.007) [21]. In another study [22], rituximab was used as first-line treatment for CLL at 375 mg/(m²·W) for 4 weeks, repeated at 6 months. The response rate after the first course of rituximab was 5 L % (CR4%) in 44 patients with CLL or small lymphocytic lymphoma. After completion of ≥1 additional course of treatment (28 cases), OR rate was 58% (CR9%). However, PFS at 18.6 months was inferior to that of patients with follicular lymphoma treated with first-line + maintenance rituximab [22]. The antitumor activity was increased when rituximab was combined with GM-CSF. The response rate was 79% (CR36%) in patients with indolent lymphoma, but 61% (CR 7%) in patients with CLL aged > 70 years.

3. Rituximab in the Treatment of Autoimmune Diseases

B lymphocytes are one of the main members of the acquired immune response. Its development process mainly goes through the stages of pre-B lymphocytes, immature B lymphocytes, initial B lymphocytes, mature B lymphocytes and memory B lymphocytes [23], and finally differentiates into bovine antibody producing plasma cells. CD₂₀⁺ B lymphocytes participate in immunity, including: production of immunoglobulin, through which the role of immunoglobulin; B lymphocyte autoantigen presentation, regulation of other immune cells; B lymphocytes affect other antigen-presenting cells such as dendritic cells, and B lymphocytes can secrete cytokines such as interleukin (IL-4, IL-10) to act on other immune cells. The abnormal interaction between B cells and T cells is crucial to the occurrence and development of immune diseases. Rituximab is a monoclonal antibody targeting CD20 molecules on the surface of B lymphocytes. It can bind to CD20 molecules on the surface of cells with a high affinity, resulting in the clearance of the bound B lymphocytes and a significant reduction in the number of B lymphocytes in the body. Currently, rituximab is mainly

used for the treatment of idiopathic thrombocytopenic purpura (ITP). Shanafelt *et al.* [24] retrospectively analyzed the therapeutic effect of rituximab in 12 refractory ITP patients (including 4 Evans syndrome patients), all of whom had received more than one course of conventional treatment before treatment and failed, and 6 of whom also received corticosteroids or other immunosuppressive agents during rituximab treatment. Results CR was found in 5 cases, and the therapeutic response was observed in both patients with and without splenectomy. Rituximab is a new biologic agent with relatively low therapeutic toxicity, which can play a certain role in the treatment of refractory ITP with severe bleeding symptoms, and can be used as an effective alternative therapy for patients who have failed to respond to conventional drugs. At the same time, its efficacy in ITP also reattracted more attention to the role of humoral immune mechanism in ITP. However, the high price of rituximab limits its wide application in clinical practice. On the other hand, its specific mechanism of action and reasonable treatment plan need further study [25] [26]. Other reports rituxan in the treatment of thrombotic thrombocytopenic purpura [27], acquired VIII factor antibody increased [28] blood coagulation disorders, caused by hemolytic anemia and refractory Greave's disease has a good response to treatment.

4. Application of Rituximab in Hematopoietic Stem Cell Transplantation

Currently, rituximab is mainly used for *in vivo* purification of autologous peripheral blood hematopoietic stem cell transplantation (APBSCT). R Z *et al.* [29] rituxan is studied in combination with large dose of chemotherapy in patients with NHL APBSCT treatment effect, the research object and IV follicular III B non-hodgkin's lymphoma and cell lymphoma patients. The author USES the rituxan, high-dose cytarabine and mitoxantrone and g-csf in peripheral blood stem cell mobilization, separation of CD_{34}^{+} cells, by PCR detection, after the separation cell tumor iconic harmony genes were negative, back to lose these cells, compared with control group, the hematopoietic reconstruction needed no difference between the amount of CD_{34}^{+} cells infusion, and to rebuild hematopoietic stem cells ability between the two groups, clinical adverse reactions and no obvious difference. X L *et al.* [30] also confirmed that combined chemotherapy with rituximab could significantly reduce the contamination of lymphoma cells in mobilized stem cells, and the clinical and molecular remission rates of patients in the rituximab group were also significantly higher than those in the control group. Galimberti *et al.* [31] 23 cases of follicular non-hodgkin's lymphoma patients APBSCT, including 13 cases with CHOP plan after chemotherapy in patients with high-dose chemotherapy alone, 10 patients using high doses of chemotherapy in combination with rituxan treatment, the results showed that application of rituxan treatment group of Bel-2/IgH rearrangement negative rate was 86%, compared with high-dose chemotherapy control graft Bel-2/IgH rearrangement negative rate is 14.3%, the former EFS 5 years was 100%, and the lat-

ter is only 41%, This suggests that rituximab is an effective treatment for patients with follicular non-Hodgkin's lymphoma. Kosmas *et al.* [32] analyzed the results of several study groups and concluded that the application of rituximab did not affect the mobilization effect of 1000 cells and did not damage the function of stem cells. *In vivo* treatment was more effective in removing residual tumor cells than *in vitro* purification of monoclonal antibody. Patients with APBSCT treated with Rituximab can quickly complete graft survival. Although neutropenia occurs in individual patients, this change is reversible and may be related to the immune response. Of course, the long-term efficacy and adverse reactions of rituximab APBSCT purification therapy *in vivo* still need further follow-up observation.

Rituximab in the treatment of malignant lymphoma malignant lymphoma is a type of malignant tumor originating in the lymphatic hematopoietic system, and is one of the top ten most common tumors in China. It can be divided into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Malignant lymphoma is a group of highly heterogeneous diseases with different clinical outcomes. Its pathological classification is complex, and the treatment principles are different for different types and different populations. Therefore, accurate assessment of the disease condition and individualized treatment should be emphasized. Chemotherapy is one of the effective methods for the treatment of malignant lymphoma, but the conventional regimen is not effective for malignant lymphoma with adverse prognostic factors. Rehwald *et al.* [33] a multicenter II period clinical study application of rituxan treatment of 166 cases of recurrent, refractory follicular non-hodgkin's Lymphoma non-Hodgkin's Lymphoma (NHL), by polymerase chain reaction detection of the Bcl-2 gene rearrangement. The overall response (OR) rate was 48%, the complete response (CR) rate was 6%, and the median time to tumor progression was 12 months. Patients with sensitive relapsing disease still had a 40% remission rate after retreatment with rituximab, and the median time to tumor progression was 17 months. A II period, according to the clinical studies have shown that rituxan for recurrent or other subtypes of CD20 positive lymphocytes as the main type of Hodgkin's lymphoma, Hodgkin's lymphoma, NL) patients is effective. Subsequent studies have found rituximab combined with chemotherapy as a first-line regimen for the treatment of NHI. Better than chemotherapy alone. Hoehster *et al.* [34] 322 patients with indolent NHL CVP treatment group and CVP were followed for rituxan maintenance treatment group after treatment of progression-free survival rates were 43% and 73% respectively, total deposit rate is 89% and 96%, respectively, differences were statistically significant, and two groups there was no statistically significant difference III or IV toxicity.

5. Rituximab for Multiple Myeloma (MM)

CD₂₀ expression in plasma cells of MM patients is low in number and density, so it is necessary to increase CD₂₀ expression on the surface of MM tumor cells in

order to effectively attack multiple myeloma cells with rituximab [35]. The experimental results of Li Juan *et al.* show that when the concentration is greater than 100 ug/ml [36]. Thalidomide combined with 16 ug/ml. The inhibition effect of thalidomide and rituximab alone on tumor cell colony formation in newly treated or relapsed refractory MM patients was higher than that of thalidomide and rituximab alone, indicating that thalidomide can increase the inhibition effect of rituximab on the growth of MM cells, which may be related to the up-regulation of CD20 expression in tumor cells by the former. From the above experiments, the clinical use of thalidomide and rituximab in the treatment of newly treated or recurrent refractory MM patients may be another direction of MM treatment.

6. Conclusion

In summary, the variable region of rituximab binds to CD₂₀ through three different mechanisms, such as antibody-dependent cytotoxicity, complement-dependent cell killing, and induction of apoptotic cell death, which cause cell destruction and lead to persistent clearance of circulating B cells [37]. Rituximab can induce a slight decrease in anti-HLA antibodies in patients with low titer antibodies [38], which is closely related to JC virus-induced progressive multifocal leukoencephalopathy [39]. Gerberg *et al.* observed the pharmacodynamics of renal transplant patients after giving a single dose of rituximab, and found that it quickly eliminated B cells and persistently inhibited B cells [40]. There are also many studies using rituximab to desensitize and treat acute antibody mediated rejection (AMR) [41] [42] [43] [44].

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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