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Therapeutic Effects of Rituximab on Burkitt Lymphoma in Children and Adolescents

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Abstract:

Burkitt lymphoma (BL) is a rapidly advancing B-cell non-Hodgkin lymphoma. It is also one of the fastest-growing human cancers. The peak age of onset is around ten years old. Children with BL are generally more likely to recover or survive without serious long-term effects. More than 90 percent of children and adolescents can be cured by receiving higher doses of chemotherapy drugs and more frequent treatments. Existing research mainly studies the optimization of treatment strategies and the exploration of new therapies, including chemotherapy, targeted therapy, immunotherapy, etc. There is also research on molecular biology, genetics, and tumor immune microenvironment, as well as factors related to patient prognosis. However, there are specific constraints related to the mechanism of drug resistance and the quality of life for individuals with BL. Rituximab is a cancer treatment approved for patients, functioning as an anti-CD20 antibody. The application of Rituximab on BL with traditional chemotherapy increased the cure rate, especially in patients with Central nervous system (CNS) lesions or refractory BL patients. This review aims to summarize the working mechanism of rituximab, the overall therapeutic effect of rituximab in patients with BL, especially children, the treatment of CNS involved in BL, the impact of rituximab on relapse rates, and the shortcomings of rituximab.

Keywords: Rituximab; Burkitt lymphoma; children; adolescents.

1. Introduction

Burkitt lymphoma (BL), a swiftly advancing B-cell non-Hodgkin lymphoma, is recognized as the most rapidly increasing form of human cancer [1]. BL has an overall 10-year survival rate of 67.8% [2]. It is more prevalent among children and teenagers, constituting 30% of lymphomas in childhood, with the highest incidence occurring around the age of 10 years old [1, 3]. At the same time, BL accounts for only 1% to 2% of adult non-Hodgkin lymphomas [1]. In addition, children and adolescents have a better prognosis than adults [4]. Children with BL are generally more likely to recover or survive without serious long-term effects [4]. Therefore, it is crucial to find reliable methods to treat BL and to allow children to receive treatment promptly to reduce the impact of BL.

More than 90% of children and adolescents can be cured by receiving higher doses of chemotherapy drugs combined with a higher frequency of treatment [1]. Currently, treatment methods such as immunotherapy, chemotherapy, radiotherapy, and surgery are available. It is a relatively traditional method of treating BL [5]. Among them, Rituximab is a noteworthy therapy. A monoclonal antibody, rituximab, targets B lymphocytes by binding to CD20 present on their surface. Through various mechanisms, these B cells are eliminated [6]. Monoclonal antibody (anti-CD20 /rituximab) therapy is now a more common treatment modality than radiation therapy [7]. However, despite these significant advances, the treatment of BL still faces challenges, for example, the long-term effectiveness of treatment, as some patients may develop relapse or drug resistance.

Therefore, this review summarizes how rituximab works and the treatment of Rituximab in children with different types of BL, including children BL with central nervous system lesions. Moreover, this review discusses the recurrence of disease using rituximab, and related side effects.

2. Mechanism of Rituximab

2.1 Anti-CD20

Rituximab is a monoclonal antibody, combining mouse and human components, designed to target CD20 specifically. Rituximab was the initial therapeutic antibody to receive approval for cancer treatment and has remained the highest-selling cancer drug for the last decade. One reason that rituximab is so popular is because it improves treatment outcomes in all B-cell malignancies [8]. Thus,

rituximab can be used widely in diseases where B cells are abnormal.

Rituximab is a monoclonal antibody that specifically aims at CD20, created through genetic engineering to be a hybrid of mouse and human components. [9]. CD20 is a transmembrane protein in pre-B lymphocytes and mature B lymphocytes, although the function of this transmembrane protein is currently uncertain. The chimeric construct of rituximab contains the variable regions of human IgG-1 and murine CD20 antibodies [9]. Research indicates that the mouse component of rituximab specifically attaches to the CD20 protein found on the surface of both healthy and cancerous B cells (Figure 1) [9]. Simultaneously, the human portion of rituximab enables it to attach to Fc receptors on immune cells. Rituximab, when attached to CD20, can trigger the death of B cells through mechanisms such as antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. As a result, there is a swift depletion of CD20-positive B cells [9]. Because BL is a rapidly progressive B-cell lymphoma, reducing B cells can help reduce the symptoms of B-cell lymphoma and control the progression of the disease. CD20 has been selected as the target for monoclonal antibody therapy because it possesses the characteristics of an ideal target. It is exclusively present in B cells, remains attached to B cells without being shed, and is expressed abundantly[1, 9]. Because of the characteristics of CD20, treatments targeting CD20 can target B cells more accurately without causing unnecessary effects on other cells. This is important in avoiding side effects and improving treatment safety. In addition, the drug can be made to act on B cells more effectively, thereby enhancing the therapeutic effect [9]. Therapeutics that target CD20 can affect B cells more permanently, thereby extending the duration of the therapeutic effect.

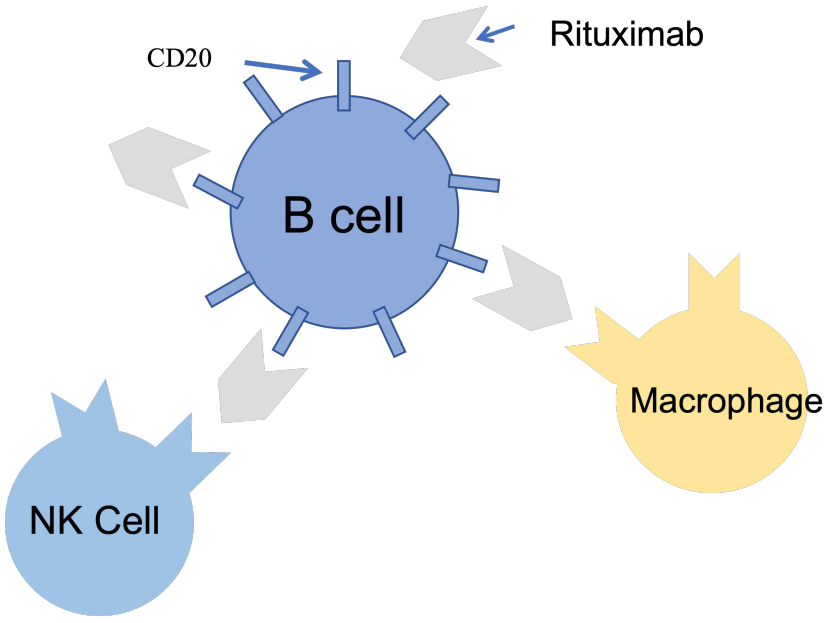

Fig. 1 Mechanisms of Rituximab on malignant B cells. Rituximab recognizes and binds to CD20 on the surface of malignant B cells, causing B cell destruction and death. Figure credit: original.

3. Rituximab on Children's BL

3.1 Overall Therapy

In terms of rituximab's general effectiveness, a meta-analysis indicates that incorporating rituximab into treatment plans for BL could potentially offer a notable improvement in survival rates when compared to using chemotherapy alone without raising the risk of mortality [10]. The use of rituximab has important clinical significance in the treatment of BL., including improving the patient's prognosis, treatment effect, and survival rate while avoiding an increase in treatment-related risks. Patients treated with rituximab experienced notably reduced rates of relapse (3 of 40 patients) compared to the relapse rate of the control group (13 of 40 patients). Thus, rituximab is likely to improve cure rates. There was a trend toward improved outcomes with rituximab-containing therapy, with 3-year PFS (74% with rituximab vs. 61% without rituximab) and 3-year OS (74% with rituximab vs. 61% without rituximab) [11].

Moreover, patients may have a lower risk of disease recurrence, slower disease progression with longer survival,

and a higher overall survival rate with the addition of rituximab compared to controls. In addition, rituximab decreased the relapse rate and demonstrated a tendency toward enhancing progression-free survival (PFS) and overall survival (OS) [11]. Therefore, rituximab is considered a very important treatment method for dealing with BL. Nevertheless, the substantial evidence and current data on the advantages of rituximab are somewhat limited, primarily because there is a scarcity of randomized clinical trials directly comparing chemotherapy alone against chemotherapy combined with rituximab. Therefore, there remains a requirement for future randomized controlled trials with a large sample size and meticulous design to validate and revise the findings of this analysis (Table 1) [10].

3.2 CNS in BL patients

In non-Hodgkin's lymphoma patients, central nervous system (CNS) involvement poses a notable, preventable risk, occurring in 5% to 10% of cases. The occurrence of CNS involvement is directly related to the pathological aggressiveness of lymphoma. In mild, less aggressive histological forms, the incidence of CNS involvement is less than 3% [12]. Whereas in very aggressive forms, such as Burkitt's lymphoma, it can be as high as 50%. Once detected, appropriate treatment can reduce or improve the patient's neurological symptoms and dysfunction, but even if treatment can improve the neurological condition, the recurrence of systemic disease may affect the patient's long-term survival. Therefore, preventing the occurrence of CNS involvement remains an important goal of treatment [12].

Studies have shown that the addition of systemic rituximab may reduce the incidence of CNS involvement [12]. Besides, rituximab can be safely used in combination with FAB C1 systemic chemotherapy and intrathecal chemotherapy [13]. Because the prognosis of children and adolescents with BL and CNS and bone marrow involvement who receive chemotherapy alone remains poor, chemoimmunotherapy with rituximab was initiated, using rituximab (375 mg/m2) in combination with the standard chemotherapy regimen previously reported in the French-American-British (FAB) BL 96 trial. Patients were classified by assessment of central pathology and cytogenetic features [14]. A total of 40 eligible patients with Burkitt's lymphoma participated in the study, 25 with leukemia and 15 with concomitant central nervous system disease or leukemia. The chemotherapy plus rituximab regimen was well tolerated. Patients experience fewer or milder adverse reactions with this treatment regimen and often receive and complete treatment effectively without the need to discontinue treatment or adjust dosage. This allows patients to receive treatment without experiencing serious side effects or complications, helping to ensure that patients receive the maximum benefit from their treatment [14]. During the combined chemotherapy and rituximab induction cycle, grade III mucositis occurred in 31% of patients, and grade IV mucositis occurred in 26% of patients. For the entire group, the 3-year event-free survival (EFS) and overall survival (OS) rates were at 90%, meaning each patient had a 90% likelihood of avoiding disease progression or death within three years of treatment initiation. The 3-year EFS/OS rate for patients with CNS disease was 93%. Patients with CNS disease have a 93% chance of not experiencing disease progression or death within three years of treatment and a 93% chance of surviving during the same period. These promising results demonstrated the good tolerability and favorable survival outcomes of the chemotherapy plus rituximab regimen and provided the basis for further international randomized studies (Table 1) [14].

3.3 Refractory BL

For those newly diagnosed with Burkitt's lymphoma, a short yet intense combination of multiple chemotherapy agents usually results in a five-year event-free survival rate of approximately 90%. On occasion, children and adolescents diagnosed with aggressive B-NHL experience recurrence or resistance to treatment. Prognoses are grim, with cure rates below 30%, and there is no established standard treatment. However, secondary treatments involving rituximab could result in a complete or partial response in 60-70% of cases [15]. For those relapsed or refractory patients, the use of rituximab-containing treatment regimens may improve the patient's condition and achieve complete or partial remission in 60-70% of cases [16]. A 14-year-old patient was diagnosed with stage III Burkitt's lymphoma, presenting with multiple tumors within the abdomen. After multidrug chemotherapy, she achieved complete remission but relapsed after six courses. Although the patient relapsed nine times in the subsequent four years and seven months, rituximab was still used as monotherapy or in combination with other drugs or local irradiation for treatment purposes. Treatment of bone metastases has been shown to be effective, leading to complete or partial remission. Therefore, chemotherapy regimens, including rituximab, may be effective in patients with multiple relapses of Burkitt's lymphoma [17]. Likewise, three children diagnosed with primary refractory or relapsed B-cell non-Hodgkin lymphoma were effectively treated using an intense chemotherapy plan alongside rituximab. These patients are currently in complete remission [16]. The use of rituximab in the treatment of B-cell NHL in children is an area of research that requires

further exploration. Combining rituximab with aggressive chemotherapy may be a potential option for inclusion in initial treatment plans. However, statistically favorable outcomes in most patients make it difficult to demonstrate improvement over current upfront treatments in controlled trials. There were no unexpected or excessive toxicities associated with rituximab plus chemotherapy. The infusion-related side effects were controllable, and none of the patients encountered the cytokine release reactions often observed in individuals with advanced illness [16]. Rituximab combined with chemotherapy has shown potential safety and efficacy in the treatment of B-cell NHL in children (Table 1). However, further research is needed to determine its exact role in upfront treatment.

Table 1. Clinical trials of rituximab treatment on children and adolescents with Burkitt lymphoma (BL)

Study design	Subjects	Treatment	Results	Reference
Systematic review and meta-analysis	A total of 646 cases.	Chemotherapy combined with rituximab group (351 cases) and chemotherapy single-agent group (295 cases).	The chemotherapy combined with rituximab group had a higher 2-year overall survival rate, a higher 2-year progression-free survival rate, and a higher complete remission rate. There was no significant difference in treatment-related mortality between the two treatment regimens.	[10]
Single-arm clinical trial	40 patients. 63% of patients had isolated bone marrow involvement, 18% had central nervous system (CNS) disease with BL, and 20% had combined CNS and bone marrow (BM) disease.	Chemoimmunotherapy regimens, including combination chemotherapy and induction cycles of rituximab	3-year Event-Free Survival (EFS) and Overall Survival (OS) were 90% and 93% for patients with central nervous system disease	[14]
Case report	Three children with primary refractory/relapsed B-cell non-Hodgkin lymphoma	Intensive chemotherapy regimens, including combination therapy with rituximab	Complete relief	[16]
Case report	A 14-year-old patient	Treated with rituximab in combination with other drugs or with local irradiation.	Treatment was with rituximab alone or in combination with etoposide, carboplatin, and etoposide chemotherapy or with local radiotherapy for bone metastases.	[17]

4. Side Effects

Fever, chills, nausea, headache, fatigue, and muscle pain are among the most common side effects of rituximab. Only a few adverse events were categorized as WHO grade III-IV. Bronchospasm and hypotension are the most severe side effects observed. The exact cause of these reactions is not entirely understood, but one theory proposes that the release of cytokines 2 and 3, or tumor lysis, may significantly contribute to their occurrence. During the initial infusion, most side effects tend to appear. Studies suggest that a substantial number of tumor cells in the bloodstream pose a significant risk factor for severe reactions. Research has indicated a correlation between the initial rituximab infusion and the onset of side effects, which is linked to the tumor load and the period between prior cytostatic treatments. [18] In addition, while rituximab is a crucial treatment choice for hematologic cancers, the likelihood of allergic reactions is significant. IgE general-

ly mediates these responses and can range in seriousness from hives to anaphylaxis. For patients who experience an allergic reaction, an alternative option is to interrupt treatment and proceed with an anti-allergic treatment such as rituximab therapy [19].

5. Conclusion

Rituximab is the first therapeutic antibody approved to treat cancer patients. Once combined with CD20, rituximab can cause B cell death or apoptosis. Therefore, it leads to the rapid depletion of CD20-positive B cells. Studies indicated that incorporating rituximab into the treatment protocol for Burkitt's lymphoma might result in a notable improvement in survival rates and decreased relapse rates compared to using chemotherapy alone without raising the risk of mortality. In patients with relapsed or refractory NHL, treatment with rituximab may improve the condition and achieve complete or partial remission in the majority of cases. Although rituximab can cause some side effects, most are mild and can be alleviated by suspending rituximab treatment and continuing anti-allergy treatment. However, despite the evidence and updated information on the benefits of rituximab being relatively strong, future large-sample, well-designed randomized trials are needed due to the lack of head-to-head randomized clinical trials directly comparing rituximab.

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