Brief Report

Rituximab Combined with Autologous Peripheral Blood Stem Cell Transplantation Improve Therapeutic Effects of Chemotherapy in Pediatric Patients with Burkitt’s Lymphoma

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Summary
We report on 2 children with Burkitt’s lymphoma accompanied by extensive extranodal involvement treated with chemotherapy and Rituximab in combination with autologous peripheral blood stem cell transplantation (Auto-PBSCT) regimens. No obvious side effects could be seen during the Rituximab therapy. Both children achieved complete remission with no relapse after being followed up for 4.3 and 4 years, respectively. Our limited experience show that Rituximab in combination with chemotherapy and Auto-PBSCT might have better therapeutic effects on Burkitt’s lymphoma of children and the side effects of Rituximab therapy is minimal and can be well tolerated.

Key words: rituximab, monoclonal antibody, stem cell transplantation, children.

Introduction
Non-Hodgkin’s lymphoma (NHL) is originated from B lymphocytes and around 95% of B-cell lymphomas that express the CD20 ‘antigen’ [1, 2]. Though NHL is usually sensitive to traditional radiotherapy and chemotherapy, the high recurrence rate and short remission period are main obstacles in its curable treatment. Recent studies showed that Rituximab is effective in many B-cell NHL (B-NHL) subtypes alone and in combination with chemotherapy and might improve the survival rate. Here, we report our experience in two children suffering from with Burkitt lymphoma stage III with extensive extranodal involvement, who were treated with Rituximab combined with the chemotherapy of Berlin-Frankfurt-Munich (BFM) protocol and autologous peripheral blood stem cell transplantation (Auto-PBSCT).

Methods
Patient 1 was a 9-year-old boy who was admitted in October 2004 because of right lower abdominal pain for 2 months and a lump in the same place for 5 weeks. Several lymph nodes were found in two sides of jaw and right cervical. The boy had moderate anemia and pale palpebral conjunctiva. An immobile, hard and rough mass, 7 cm × 11 cm in diameter in the right lower abdomen was observed. His liver could be touched 3 cm below xiphoid process margin. Laboratory test data showed that lactate dehydrogenase (LDH) 273 U/l; viral capsid antigen (VCA)-IgM and early antigen (EA)-IgG of Epstein-Barr (EB) virus were positive. Extensive carcinomas in the lower abdomen, retroperitoneally and...
in the ascites were detected with magnetic resonance imaging (MRI) examination (Figs 1 and 2).

Patient 2 was a 5-year-old boy admitted to our hospital in March 2005 with right face swelling for 20 days. On physical examination, slightly brachy-chronic breath and a visibly oncotic abdomen were found, and a mass was palpable in the lower abdomen. His face was asymmetrical with the right face and eye oncotic than the opposite side. A lump extensively offended acroteric tissue in right exognathion, tumors shifted to peritoneum and abdominal dropsy in abdominal cavity was detected on his exognathion and abdominal MRI scan (Figs 3 and 4).

Pathological results of these two patients confirmed the diagnosis of Burkitt’s lymphoma (stage III), and >90% of the blasts were CD20 positive.

The two children were treated according to B-NHL BFM-90 protocol. After finishing the courses of phase V plus AA and BB blocks, the abdominal MRI examination indicated that the original lump in abdominal cavity and retroperitoneal intumescent lymph node of the Case 1 disappeared (Figs 5 and 6), LDH was decreased to 104 U l⁻¹ and complete remission (CR) obtained. With regard to Case 2, after the second case finished the courses of phase V plus AA and BB blocks, his abdominal circumference was markedly reduced, and his liver, gall-bladder and spleen were normal and abdominal dropsy was obsolescent, LDH was reduced to 177 U l⁻¹. However, his right jaw was still oncotic and there were many intumescent lymph nodes on both sides of the carotid sheath (Figs 7 and 8), thus achieving only partial remission (PR). For the extensive extranodal invasion at onset and merely PR reaction
to the chemotherapy in the two cases, after one or two additional courses of chemotherapy, including phase AA/CC blocks, cytarabine (Ara-C) and cyclophosphamide (CTX) as the consolidation treatment, the Auto-PBSCT was performed with Rituximab-conditioning regimens. Table 1 shows the programs of chemotherapy and conditioning regimens of the patients.

Rituximab dissolved in normal saline was given to the two patients at a dose of 375 mg m$^{-2}$ by intravenous infusion and sustained for 4-5 h in hematopoietic stem cell transplantation (HSCT) conditioning on Day 1. The infusion speed was 50 mg h$^{-1}$ during the first hour and gradually rose to 100 mg h$^{-1}$. Rituximab was given to both children at Day 1 before Auto-PBSCT, and one patient was given an additional Rituximab during chemotherapy. To prevent the toxicity of Rituximab, Benadryl, Dexamethsone and Ibuprofen (Motrin) were given 30 min before administering Rituximab.

Antibiotics, intravenous immunoglobulins (IVIG), heparin, prostaglandin E and polyene phosphatidylcholine (Essentiale as the trade name) were used to prevent the complication relevant to transplantation such as infection and hepatic venous obstruction syndrome.
Results

After transplantation, the WBC count of the two children began to rise on the Days 14 and 17, respectively. Bone marrow examination showed recovery of granulocytes on the Day 30 after Auto-PBSCT. The first boy maintained CR, and the second boy was normal but a slightly intumescent lymph node in the deep part of both sides of the neck could be noted using MRI. At present, both children sustain CR in the past 4.3 and 4 years, respectively.

Side effects such as fervescence and hypersensitivity could be avoided by the premedication of Benadryl, Dexamethsone and Ibuprofen prior to Rituximab treatment.

Myelosuppression occurred after the treatment of Rituximab combined with chemotherapy and Auto-PBSCT. The ratio of CD20 positive cells in peripheral blood of the second case assayed by flow cytometry dropped from 21.77 to 0.11% after Rituximab therapy. The infusion of G-CSF, platelet and red blood cells helped to enhance hematogenesis and lessen complications such as bleeding and infections. While the active use of antibiotics and IVIG (at a dose of 400–500 mg kg⁻¹, once a week after 2 months of Auto-PBSCT) could decrease the incidence of infection and limit their severity.

Discussion

Rituximab, an anti-CD20 monoclonal antibody, is a chimera human/mouse antibody. It was first licensed to treat indolent lymphoma by the United States Food and Drug Administration (FDA) in 1997 [3]. Rituximab can bind to CD20 and inhibit B-cell proliferation. It can also induce antibody- and complement-mediated cytotoxicity [4, 5]. The application of Rituximab can induce apoptosis of cells [6, 7] and increase the sensitivity of tumor cells to chemotherapy [8–10]. It brings hopes for boosting the curative effect in NHL.

At present, Rituximab is widely used to treat all forms of NHL. In the international trial that Pfreundschuh et al. [11] carried out, they used Rituximab in combination with the CHOP protocol to treat 350 young patients who had diffused large B-cell lymphoma (DLBCL). The rate of CR was 86% and 3-year survival rate of non-disease was 79%.

These two parameters were better than that in the control group, which was only treated with CHOP. These results indicated that Rituximab in combination with CHOP (R-CHOP) could significantly increase the survival rate of young patients with DLBCL. Another report from Czuczman et al. [12] showed that the total effective rate and CR rate in a multi-center II phase clinical study using R-CHOP to treat 40 patients with follicular lymphoma (FL) was 100 and 87%, respectively, during 9-years follow-up visit. It indicated that combination with Rituximab could significantly extend the disease-free survival of newly diagnosed or relapsing patients.

Although Auto-PBSCT can treat NHL efficiently, minimal residual disease (MRD) cannot be avoided after transplantation. Therefore it is very important to take measures to eliminate tumor cells before transplantation. The phaseI/II clinical trials of Press et al. [13] indicated that the 2-year non-progressive survival rate, or total survival rate, by using Rituximab in combination with etoposide (VP16), CTX and Auto-PBSCT to treat relapsing NHL, was higher than that of control groups pretreated by total body irradiation, VP16 and CTX (68 and 83%, 36 and 53%, respectively). Magni et al. [14] who used chemotherapy in combination with Rituximab and Auto-PBSCT to treat 15 relapsing patients with CD20 positive mantle cell lymphoma (MCL) and follicular lymphoma (FL) and achieved a high curative effect and 93% of patients maintained CR after 14-months follow-up after transplantation.

In our study, a curative effect was obtained using Rituximab in combination with chemotherapy and Auto-PBSCT in the treatment of two children with B-cell lymphoma (stage III); both achieved CR. Using Rituximab as a conditioning agent one day before Auto-PBSCT might thus be very important for specifically clearing lymphoma cells [15].

The side effects caused by Rituximab medication were mainly infusion-related reactions. These symptoms usually include fever and shakes [16], facial flush, angioedema, nausea, urticaria and so on [17–19]. A few patients may show aggravation of aforesaid symptoms accompanied by hypotension and bronchial spasm. These symptoms mostly occur during the first infusion, especially within the first or
the second hour. By appropriate use of diphenhydramine, dexamethasone and Ibuprofen before Rituximab application, no obvious side effects were seen in the two cases of our study. Rituximab could partly reduce the number of B lymphocytes in the peripheral blood of the patients and it may increase the incidence of Rituximab treatment of related infectious problems. CD20 positive cells in the peripheral blood in one of our patients dropped from 21.77% to 0.11% on Day 52 after Rituximab infusion, there were no severe infective symptoms, but slight alimentary infections because of the actively usage of IVIG, and that could be controlled effectively by application of antibiotics.

Our limited clinical experience thus shows that Rituximab may provide a new curative treatment for patients with NHL because of its high tolerance and selective effect on B cells. However, this notion still requires large-scale clinical exploration and observation in pediatrics patients. Moreover, the clinical application of Rituximab may be restricted by the economic conditions of the patients, especially in developing countries because of the high costs involved.

References