Rituximab combined with autologous hematopoietic stem cell transplantation for treatment of non-Hodgkin lymphoma in 6 patients☆

Sun Zhi-qiang, Wang Ji-shi, Lu Ying-hao, Xie Run-lan, Long Zheng-mei

Department of Hematology, Affiliated Hospital of Guiyang Medical College, Guiyang 550004, Guzhou Province, China

Sun Zhi-qiang☆, Doctor, Associate chief physician, Department of Hematology, Affiliated Hospital of Guiyang Medical College, Guiyang 550004, Guzhou Province, China
zhqsun69@163.com

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Abstract

BACKGROUND: Rituximab single or in combination with CHOP regimen for treatment of CD20-positive non-Hodgkin lymphoma has achieved good curative effects. Autologous hematopoietic stem cell transplantation (AHSCT) has been shown to improve the curative effects and increase survival rate of patients with non-Hodgkin lymphoma. However, the curative effects of these two methods remain disputed.

OBJECTIVE: To investigate the efficiency of rituximab in combination with AHSCT on CD 20-positive non-Hodgkin lymphoma.

METHODS: Six patients with CD 20-positive non-Hodgkin lymphoma (stage IV) underwent AHSCT and rituximab administration. 375 mg/m^2 rituximab was intravenously administered 2–4 times prior to AHSCT, twice prior to and after peripheral blood stem cells mobilization and preprocessing, respectively, as well as once every 3 months after AHSCT.

RESULTS AND CONCLUSION: The mean number of mononuclear cells and CD 34-positive cells was 5.13×10^{-8}/kg and 4.75×10^{-6}/kg, respectively. Following AHSCT, all 6 patients presented normal hematopoietic functions, neutrophils exceeded 0.5×10^{-9}/L at 9–15 days and blood platelet counts exceeded 20×10^{-9}/L at 12–19 days. Hemorrhagic cystitis, interstitial pneumonia, cytomegalovirus infection, or hepatic venous obstruction was not observed during the whole process of AHSCT in each patient. At 6–32 months, patients completely recovered. These results indicate that rituximab in combination with AHSCT is a good method for treatment of CD20-positive non-Hodgkin lymphoma and rituximab maintenance therapy could prevent disease recurrence.

INTRODUCTION

After conventional therapy, some non-Hodgkin lymphoma patients survive long time, but with high-risk prognosis factors. Refractory or recurred lymphoma possesses poor curative effects. Autologous hematopoietic stem cell transplantation (AHSCT) has been recently shown to be an important method to treat or heal non-Hodgkin lymphoma. AHSCT can improve the curative effects and increase survival rate of patients with non-Hodgkin lymphoma. Rituximab single or in combination with CHOP regimen for treatment of CD20-positive non-Hodgkin lymphoma has achieved good curative effects. Rituximab in combination with CHOP and AHSCT for treatment of non-Hodgkin lymphoma have markedly reduced the recurrence of non-Hodgkin lymphoma.

This paper reported a successful treatment of CD20-positive non-Hodgkin lymphoma using rituximab combined with AHSCT.

CASE INTRODUCTION

General data

Six patients with CD 20-positive non-Hodgkin lymphoma (stage IV) admitted to the Affiliated Hospital of Guiyang Medical College between August 2006 and May 2009 were included in this study. These patients, comprising 4 males, 2 females, averaging 44.6 years of age (range 30–57 years old), corresponded to the WHO diagnostic criteria of non-Hodgkin lymphoma. Of them, 5 were diffuse large B-cell lymphoma, 1 small lymphocytic lymphoma, 3 were previously untreated, and 3 were patients with recurred non-Hodgkin lymphoma. Written informed consent regarding treatments and risk was obtained according to *Administrative Regulations on Medical Institution* formulated by the State Council of China[1]. Therapeutic regimen was approved by Hospital Medical Ethics Committee.

Therapeutic methods

For patients who were previously untreated, four courses of treatment involving rituximab combined with AHSCT were used. Precisely, on day 1: rituximab (375 mg/m^2, i.v.); on day 2: cyclophosphamide (750 mg/m^2, i.v.); on day 3: vincristine (2 mg/m^2, i.v.); on days 2–6: prednisone (100 mg/d, oral administration). For patients with recurred non-Hodgkin lymphoma, two courses of treatment involving rituximab combined with ICE regimen. Precisely, on day 1: rituximab (375 mg/m^2, i.v.); on days 2–4: VP-16 (100 mg/m^2, i.v.); on day 3: carboplatin (300 mg/m^2, i.v.).

Mobilization, collection and cryopreservation of peripheral blood stem cells

A regimen comprising cyclophosphamide (4.0 g/m^2, administered through two sessions) and recombinant human granulocyte colony-stimulating factor (rhG-CSF) was used. For patients who failed in mobilization procedure, a CE regimen comprising cyclophosphamide (2.0 g/m^2, administered through two sessions) and etoposide (500 mg/d, for 2 consecutive days) was employed. When peripheral white blood cells were less than 1×10^9/L, rhG-CSF was subcutaneously administrated at a dose of 300 μg/d. When white blood cell counts recovered to 5×10^9/L, peripheral blood hematopoietic stem cells were isolated through the use of CS-3000 Plus blood cell separator (Baxter Healthcare, USA), and

collected through one or two sessions, each 10.0–14.0 L of circulated blood. Peripheral blood mononuclear cells (1.70–10.20)×10^8/kg receptor body mass and CD 34-positive cells (2.10–14.40)×10^6/kg receptor body mass were harvested. The collected stem cell suspension and cryoprotectant (containing 12% hetastarch and 10% dimethyl sulfoxide) were mixed at a proportion of 1:4 and then placed at –80 ℃ for future use.

Pre-processing scheme

The BEAM pre-processing scheme was employed. Precisely, on day 1: Mel (140 mg/m^2, i.v.); on days 2–5: VP-16 (200 mg/m^2, i.v.) and Ara-C (200 mg/m^2, i.v.); on day 6: BCUN (300 mg/m^2, i.v.). Then, autologous hematopoietic stem cell transplantation was performed. On days 1 and 8, rituximab (375 mg/m^2, i.v.) was used.

Supportive treatment and complication prevention

Prior to surgery, patients received general physical examinations, and removal of infection foci involving oral cavity, auricular meatus, nasal passage, crissum, and respiratory tract. Following chlorhexidine (1: 2 000) bath, patients underwent pre-processing in the 100 laminar flow room. Precisely, strict reverse isolation measures were performed until white blood cell counts reached 5.0×10^9/L. At the same time, drug was routinely used to prevent the infection of pathogenic microorganism, including bacteria, fungus, Pneumocystis carinii, and virus. If infection occurred, anti-infective therapy was immediately performed after collection of etiological specimen, and corresponding treatments were given according to etiological results. On day 3 after transplantation, G-CSF [(5.0–10.0 μg/kg per day, s.c.) till surviving, and hemoglobin was maintained > 70 g/L and blood platelet counts > 20×10^9/L. Prostaglandin E1 (20 μg/d) was used to prevent hepatic venous occlusion and mesna injection for hemorrhagic cystitis.

Disease condition monitoring

Disease condition was periodically assessed, including whether hematopoietic and immunological functions recurred. Rituximab (375 mg/m^2, i.v.) was administered once every 3 months, for 1 or 2 years in succession, to prevent relapse.

RESULTS

Efficacy of peripheral blood stem cell mobilization and collection

Peripheral blood stem cells were collected once or twice at 12–14 days after chemotherapy. Results showed that the mean number of mononuclear cells in the collected samples was 5.13×10^{-8}/kg and that of the CD 34-positive cells was 4.75×10^{-6}/kg.

Hematopoietic function recovery following AHSCT

Following AHSCT, all 6 patients presented normal hematopoietic functions, neutrophils exceeded 0.5×10^{-9}/L at 9–15 days and blood platelet counts exceeded 20×10^{-9}/L at 12–19 days.

Drug adverse reactions and AHSCT complications

Hemorrhagic cystitis, interstitial pneumonia, cytomegalovirus infection, or hepatic venous obstruction was not observed during the whole process of AHSCT in each patient.

Assessment of therapeutic effects

At 6–32 months, all patients were in complete remission.

DISCUSSION

AHSCT has been widely accepted in the treatment of relapsed or refractory invasive lymphoma. Considerable studies support a viewpoint that autologous transplantation can be used as a standard treatment, in particular for the patients with relapsed lymphoma who are sensitive to chemotherapy. Evidence exists that AHSCT, as a first-choice therapeutic intervention, can reduce 40%–50% of tumor invasion, and 18%–25% of patients with relapsed lymphoma receive the second complete remission. Compared with conventional treatment, AHSCT increases long-term survival rate over 30%, enhances the curative effects of non-Hodgkin lymphoma, reduces relapse, and prolongs healthy survival period[2-3]. But AHSCT as a first-choice method for treatment of high-risk, invasive lymphoma remains disputed. Greb *et al*[4] performed a meta analysis of 2 728 patients with invasive non-Hodgkin lymphoma and concluded no difference between AHSCT and conventional therapeutic methods in terms of non-reduced survival rate and total survival rate. This occurs because 40%–70% of non-Hodgkin lymphoma patients unavoidably suffer from relapsed lymphoma and die following AHSCT, and relapsed lymphoma is frequently observed in patients who present with tiny residual disease foci *in vivo* and/or receive tumor cells contaminated AHSCT.

Rituximab, a chimeric murine/human monoclonal antibody, kills tumor cells by antibody-dependent cells mediated cytotoxicity, complement-dependent cytoxic effect, inducing tumor cell apoptosis, interfering anti-apoptotic approach, and increasing lymphoma cell sensitivity to chemotherapy[5]. Rituximab combined with chemotherapy has been widely used to treat CD20-positive non-Hodgkin lymphoma and acquire satisfactory curative efficacy.

Rituximab in conjunction with AHSCT for treatment of CD20-positive non-Hodgkin lymphoma has recently become a rapidly growing area of research. Several studies[6-7] have demonstrated that rituximab chemotherapy combined with AHSCT for treatment of progressive non-Hodgkin lymphoma can acquire satisfactory healthy survival rate and long-term survival rate. Umberto *et al*[8] recently reported that rituximab chemotherapy plus AHSCT for treatment of progressive non-Hodgkin lymphoma had acquired 70% 4-year healthy survival rate, and 80% 4-year total survival rate, and the control results are 44% and 54% respectively.

Michele *et al*[9] used intensive chemotherapy, rituximab infusion, and AHSCT to treat 15 patients with CD20-positive mantle cell or follicular lymphoma and acquired good therapeutic efficacy. The negative-tutnning rate of IgH gene rearrangements was 93% and at 14 months after AHSCT, 93% of patients were still in complete remission. Christian *et al*[10] reported similar results. The present study used rituximab infusion and AHSCT to treat 6 patients with CD 20-positive non-Hodgkin lymphoma and obtained good short-term curative effects. These results indicate that rituximab combined with AHSCT is presently an ideal choice for

treatment of CD20-positive lymphoma.

Rituximab infusion in combination with chemotherapy mobilization and *in vivo* purging has been studied. For example, Michele *et al*[9] reported 15 patients with lymphoma invovling bone marrow and received anti-CD20 monoclonal antibody rituximab. Results revealed that the CD34-positive cells harvested from the patients who received both chemotherapy and rituximab were polymerase chain reaction-negative in 93% of cases (versus 40% of controls). Belhadj *et al*[11] treated 11 relapsed B cell non-Hodgkin lymphoma first with rituximab, then a mobilization chemotherapeutic regimen, followed by peripheral blood stem cell transplantation. Results revealed that harvests were free of PCR-detectable molecular marker in 9 cases. There is evidence that following in vitro purging with rituximab, 80%–90% of stem cell harvests from patients with PCR-negative peripheral blood were contaminated with lymphoma cells[9], which presumes not to produce influences on mobilization and collection of peripheral blood stem cells, although related laboratory examinations are not performed. Brugger *et al*[12] reported that rituximab consolidation after AHSCT can prevent repalse by clearance of minimal residual disease in patients with follicular or mantle cell lymphoma. The present study used rituximab (375 mg/m^2, i.v.) once every 3 months for 1–2 years in succession to prevent relapse as far as possible. During the whole follow-up period, all patients were in complete remission, with marked curative effect. But long-term curative efficacy needs to be further investigated. In addition, whether rituximab can inhibit organism's immune function, increase function is also the key part in future work.

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自体造血干细胞移植联合利妥昔单抗治疗非霍奇金淋巴瘤 6 例☆

孙志强，王季石，卢英豪，谢润兰，龙正美(贵阳医学院附属医院血液科，贵州省贵阳市 550004)

孙志强☆，男，1969 年生，贵州省遵义市人，汉族，2001 年贵阳医学院毕业，博士，副主任医师，主要从事干细胞移植方面的研究。

摘要

背景：利妥昔单抗单用或联合 CHOP 方案化疗治疗 CD20 阳性非霍奇金淋巴瘤已取得较好疗效，非霍奇金淋巴瘤经自体造血干细胞移植治疗同样可以提高患者的疗效和生存率，而将两种方法联合的效果尚存在争论。

目的：探讨自体造血干细胞移植联合利妥昔单抗对 CD20 阳性非霍奇金淋巴瘤的有效性。

方法：对 6 例 CD20 阳性非霍奇金淋巴瘤Ⅳ期患者进行自体造血干细胞移植的同时，联合使用利妥昔单抗，分别于移植前给予 2~4 次，动员和预处理前后各 2 次，移植后每 3 个月维持治疗 1 次，利妥昔单抗用量为 375 mg/m^2 静滴。

结果与结论：平均采集单个核细胞数为 5.13×10^{-8}/kg，CD34$^+$细胞数为 4.75×10^{-6}/kg。6 例患者自体造血干细胞移植后，造血功能均恢复顺利，中性粒细胞计数大于 0.5×10^{-9}L^{-1} 为移植后 9~15 d，血小板计数大于 20×10^{-9}L^{-1} 为移植后 12~19 d。6 例患者在移植过程中均未发生出血性膀胱炎、间质性肺炎、巨细胞病毒感染和肝静脉阻塞等并发症。利妥昔单抗使用过程中，无发热、寒战、皮疹等不良反应发生。移植后 6~32 个月，患者均处于完全缓解状态。提示自体造血干细胞移植并利妥昔单抗治疗 CD20 阳性非霍奇金淋巴瘤是一种较好的方法，可维持治疗效果，有利于防止复发。

关键词：非霍奇金淋巴瘤；利妥昔；化疗；移植；自体造血干细胞；干细胞

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