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Original Article

Rituximab as salvage therapy for refractory sclerodermatous chronic graft-versus-host disease

利妥昔單抗作為難治性硬皮病樣慢性移植物抗宿主病的搶救治療

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While various different treatments have been suggested for the treatment of sclerodermatous graft-versus-host disease (ScGVHD), there is still no accepted standard for "salvage therapy" for refractory ScGVHD. We reviewed the clinical outcome of 14 patients suffering from refractory ScGVHD with refractory to at least 3 lines of immunosuppressive therapy and who received intravenous infusions of rituximab (375 mg/m^2 per infusion) at weekly intervals for 4 weeks. Response to rituximab was evaluated after three months following the final infusion in accordance with National Institute of Health criteria. Median follow-up after rituximab was 20 months (range, 0.4-38.4 months). The overall response rate at was 43%. No major toxic events were seen related to rituximab.Rituximab appears to work well in the treatment of refractory ScGVHD and further trials in patients with early stage of this disease ought to be considered.

儘管已有各種不同治療方法建議用來治療硬皮病樣移植物抗宿主病，但對於難治性的硬皮病樣移植物抗宿主病仍然沒有公認的「補救治療」標準。 我們回顧了此病14例難治性個案（至少對三種免疫抑制治療無效）的臨床結果。患者每週靜脈輸注利妥昔單抗（每次輸注375 毫克/平方米），持續四週；我們根據美國國立衛生研究院（NIH）標準，在最終輸注後三個月對利妥昔單抗的反應進行了評估。利妥昔單抗後的中位隨訪時間爲20個月（範圍爲0.4-38.4個月），整體有效率爲43% 。沒有發現與利妥昔單抗有關的重大藥物毒性事件。利妥昔單抗似乎在治療難治性硬皮病樣移植物抗宿主病方面效果良好，可繼而考慮在此病早期患者作進一步的試驗。

Keywords: Haematopoietic stem cell transplantation, rituximab, salvage therapy, sclerodermatous chronic graft-versus-host disease

關鍵詞：造血幹細胞移植，利妥昔單抗，搶救治療，硬皮病樣慢性移植物抗宿主病

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Introduction

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) has become accepted as a potentially curative treatment for both malignant and non-malignant haematological diseases. However, its therapeutic potential is offset by high morbidity and mortality as a result of the procedure.

Chronic graft-versus-host disease (cGVHD) is one of the main causes of post allo-HSCT morbidity

and mortality affecting 25% to 40% of survivors in the long term.[1] This problem is being encountered more and more now as upper age limit for patients receiving allo-HSCT is increasing. Other factors increasing the frequency of cGVHD are use of alternative donors, peripheral blood stem cells (PBSC) and donor lymphocyte infusions (DLI).[2]

The immunopathogenesis of cGVHD is mediated in part by helper T lymphocyte 2 (Th2) cells, mimicking a syndrome characterised by immunodeficiency and an autoimmunity.[3] cGVHD is a disease that affects practically all the organs and tissues of the body, resulting a notable increase in T lymphocyte infiltration and collagen deposition in the tissues of the targeted organ. In more than 90% of patients it affects the skin, frequently leading to long-term problems and consequences. These can be cosmetic or functional and some can be life-threatening. The most widely encountered pathological change in patients with cGVHD is sclerotic skin lesions known as sclerodermatous cGVHD (ScGVHD). ScGVHD manifests clinically in the form of sclerodermatous lesions, lichenoid lesions, pigmentation disorders (e.g., hypopigmentation and hyperpigmentation), and the appearance of leopard-skin (well-delimited and widespread hyperpigmentated macules.[4]

A recent prospective study of 909 HSC Trecipients reported 10% cumulative incidence of cutaneous sclerosis after HSCT at two years.[5] In advanced stages, cutaneous sclerosis is known to cause joint contractures, chronic skin ulcers and thoracic encasement leading to pulmonary insufficiency. Cutaneous sclerosis is a known risk factor for patients with cGVHD, and its potential for affecting transplant outcomes has been reported.[6] Other factors linked to a greater risk of cutaneous sclerosis include total body irradiation as part of the conditioning regimen and use of peripheral blood as grafts.[6,7]

A combination of cyclosporin (CSA) and corticosteroids (CS) is the most common first-line treatment for cGVHD. However, about 40% of patients are expected not to respond to this combination. CS-resistant cGVHD is a particularly difficult complication known to be associated with high rates of morbidity and 26% mortality.[8] While various different treatments have been suggested for the treatment of cGVHD such as thalidomide, daclizumab, mycophenolate mofetil (MMF), pentostatin, imatinib and etanercept, as well as immunomodulating procedures such as UV radiation, psoralen, extracorporeal photopheresis (ECP), and T-cell-depleting antibodies, their results have been inconclusive and there is still no accepted standard for "salvage therapy" for refractory cGVHD.[9,10]

One reason why cGVHD therapy has not been improved is the fact that its pathophysiology is not fully understood. In the past, GVHD was considered mainly due to toxicity mediated by T-cells, which is why strategies for its prevention and treatment have focused mainly on blocking T-cell function. However, recent studies on animals and humans have shown that B cells might play a key role in the biology of cGVHD.[11] Other studies have shown a correlation between cGVHD and the allo-antibodies associated with minor histocompatibility antigens associated with the Y-chromosome in sexually mismatched allogeneic stem cell transplantations and that donor-derived B cells could induce cGVHD in mice.[12,13] Another correlation with development and severity of cGVHD are high levels of B cell-activating factor of the tumour necrosis factor family (BAFF).[14,15] Finally, these data indicate that B-cell targeted drugs such as rituximab may be an effective way of treating cGVHD, especially in steroid-refractory cases.

Being a chimeric monoclonal antibody that binds with CD20 antigens on the surface of B cells, rituximab is believed to prompt cell lysis and apoptosis. Although rituximab is commonly used to treat B-cell lymphomas and chronic lymphocytic leukemia with great success, recent studies have shown it may be also effective in treating refractory cGVHD with response rates of almost 70% according to a meta-analysis.[16]

We decided to perform a retrospective study in order to determine how effectively and safely rituximab works as a salvage option in the treatment of steroid-refractory ScGVHD.

Materials and methods

A total of 14 patients suffering from steroid-refractory ScGVHD who received rituximab between June 2014 and October 2016, were included in the study. All the patients were diagnosed with moderate to severe ScGVHD and refractory to at least three lines of immunosuppressive therapy. Four patients had also clinically diagnosed bronchiolitis obliterans syndrome (BOS). Prednisone was given as the first line of treatment while later treatments used several types of immunosuppressive approaches like MMF, CsA and ECP. All the patients received CsA with short-term methotrexate for GVHD prophylaxis.

The cGVHD was diagnosed was in accordance with current National Institute of Health (NIH) criteria.[17] All patients had at least one diagnostic sign of cGVHD or at least one distinctive manifestation confirmed by biopsy or other laboratory tests. NIH consensus criteria were also applied in evaluating staging/grading and response to therapy of cGVHD.[17,18] Sclerotic cutaneous incidents were confirmed by skin biopsy in all patients. The diagnosis of BOS was made as a result of classical clinical symptoms, computed tomography scan of the chest and lung functional test evaluation but was not supported by histology.

Monoclonal anti-CD20 (Rituximab (MabThera), Roche, Milan, Italy) was administered to all the patients. Intravenous rituximab 375 mg/m^2 infusions were given every week for four weeks. Before the infusion of rituximab all patients were pre-medicated with paracetamol, antihistaminic and prednisolone for prophylaxis of infusion-related reactions. All patients received prophylactic trimethoprim/sulfamethoxazole and valacyclovir for prevention of Pneumocystis Jirovecii and Herpes Simplex Virus infections, respectively. CMV seropositive patients and patients with a CMV-seropositive donor had routine CMV surveillance and received preemptive ganciclovir, if indicated.

Patient's response to rituximab was evaluated three months after the final infusion. Response was defined according to NIH Consensus Development Project criteria.[18] All analyses were performed using SPSS software version 22. This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board.

Results

The patients' clinical characteristics are detailed in Table 1. We included eight males (57%) males and six females (43%). Median age of the study cohort at the time of transplantation was 37 years (range, 17-58 years). All patients received peripheral blood-derived stem cells. The donor source was 10/10 HLA-matched sibling and unrelated donor in 13 and one patient, respectively. Ten patients (71%) were in remission of at the time of allo-HSCT. The great majority (n:12; 78%) of the cohort were treated with myeloablative conditioning. Four male patients received allo-HSCT from a female donor. In one patient, cGVHD occurred after the administration of donor lymphocytes (DLI).

Rituximab was offered at least as fourth or later line of therapy in all cases (Six patients were given rituximab as fourth-line therapy, seven as fifth-line and one as sixth-line). Baseline immunosuppressive therapy was continued during the period in which rituximab was given but steroids were not used in any patient, except for the pre-infusion administration of steroids for prevention of infusion-associated reactions. The median time from transplantation to the first infusion of rituximab was 21 months (7-50 months). Treatment of one patient was stopped after the first infusion as the patient deteriorated

anddied as a result of cGVHD before the next infusion could be given.

The overall response rate was 43% with one CR (7%) and 5 PR (36%). The median follow-up of living patients was 20 months (0.4-38.4 months). During the study period three of the 14 patients died: one from relapsed disease, one from pulmonary thromboembolism and one from cGVHD progression. The patients who died before evaluation of treatment response were treated as no response (NR). The NR rate was 57% with no patients exhibiting progressive disease (PD). No improvement could be seen in the lung manifestations of cGVHD.

Four patients developed grade I-II infusion-related symptoms following administration of rituximab, no major toxic events as a direct result of rituximab were seen.

Table 1. Clinical features of patients

Number of patients	14
Median age (range:years)	37 (17-58)
Male patients (no.)	8
Female patients (no.)	6
Diagnosis	
Acute myeloid leukaemia	4
Acute lymphoblastic leukaemia	7
Multiple myeloma	1
Hodgkin's lymphoma	1
Myelodysplastic syndrome	1
Donor: sibling/unrelated	13/1
Conditioning regimens: myelo-ablative/Nonmyelo-ablative	11/3
Stemcell source: bone marrow/ peripheral blood	0/14
cGVHD: moderate/severe	6/8
Median duration from transplantation to Rituximab, months (range)	21 (7-50)
Median number of failed treatment lines before Rituximab (range)	3, 6 (3-6)
Previous treatments:	
Prednisone	14
Cyclosporine	14
Photopheresis	12
Mycophenolatemofetil	8
Autologous stem cell transplant	1
Median follow-up after Rituximab, months (range)	20 (1-38)

Abbreviation: cGVHD: chronic graft-versus-host disease.

Discussion

Chronic graft-versus-host disease is a syndrome characterised by abnormal immune regulation, inflammation and fibrosis. One particular form of cGVHD is sclerodermatous cGVHD (ScGVHD) characterised by cutaneous sclerosis. This form mainly presents with fibrosis of the skin and fascia. Since the pathophysiological mechanisms behind the development of cutaneous sclerosis are not well understood, treatment has consisted of the empirical use of medications that have been approved for other disorders whose pathogenesis also involve fibrosis, abnormal immune regulation or inflammation. Management of ScGVHD is difficult with evidence limited to reports from uncontrolled single-arm studies of second-line or subsequent treatments,[19,20] retrospective studies,[21] or reviews.[16,22]

ScGVHD is similar in many respects to systemic sclerosis with skin fibrosis being its main characteristic.[1,4] Numerous studies have reported a correlation between cGVHD and autoimmune markers.[23,24] Auto antibodies are the result of B-cell hyperactivity brought on by donor T cells in cGVHD and by auto-reactive T cells in autoimmune disease.[25,26] Sato et al hypothesised that B-cell hyperactivity might not simply be a sign of T-cell activation but may also be a co-factor in the development of fibrosis in systemic sclerosis. Common to patients with systemic sclerosis are a high number of native B cells, recurring

hyperactivity in memory B cells, and increased production of interleukin-6, which in turn precipitates the synthesis of collagen and extracellular matrix.[27] Due to the high number of immunological similarities with systemic sclerosis, it seems to be logical to apply this correlation to ScGVHD, linking autoimmunity and skin fibrosis.[23,28,29] Another theory suggests that the sclerotic phenotype is the result of impaired donor B-cells. Increasingly more data suggest that high levels of BAFF following allo-HSCT result in survival of allo- and auto-reactive B-cells leading to continual activation of B-cell transmitter paths in cGVHD.[15,30] Recent studies from animal models also support the pathogenic role of B-cells in cGVHD.[31] In light of these findings, it is not surprising to suggest that rituximab and similar B-cell targeting therapies may be effective in treating ScGVHD.

Rituximab's potential as therapy for cGVHD emerged quite by accident when a patient who was no longer taking steroids for immune thrombocytopenia also showed improvement of his cGVHD while being treated with rituximab.[32] Since then, rituximab's potential therapeutic value in certain cGVHD manifestations, particularly its effectiveness in treating skin problems such as scleroderma, has been reported in several prospective and retrospective studies.

Two small studies were carried out on eight and six patients in 2003 and 2004, respectively, reporting specific organ response rates of 50% and 80%, predominantly in patients with skin problems.[26,33] Cutler et al carried out the first prospective Phase I-II study indicating the effectiveness of rituximab in 21 patients with an objective response seen in 70% of patients. The patients most likely to respond to rituximab are those with cutaneous or musculoskeletal manifestations of cGVHD. During the study period antibody titres against Y-chromosome encoded minor HLA-antigens decreased. However, titres against tetanus and EBV remained constant.[19] In the wake of this prospective study several retrospective studies were published in which more than 100 patients reported good tolerability with response rates ranging between 50% and 80%.[21,34-37] In the majority of these studies, rituximab were applied as second line therapy and a weekly dose of 375 mg/m^2 for four to eight weeks. Conversely, von Bonin et al noted similar effectiveness with an average response rate of 69% including three patients (23%) with CR when using significantly lower doses (50 mg/m^2/week) over four weeks in 11 patients with steroid resistant cGVHD and in two patients with post-transplant autoimmune disorders (glomerulonephritis and immune-thrombocytopenia).[38] A large prospective study involving 37 patients,[16] as well as a meta-analysis covering 111 patients including three prospective and four retrospective studies,[22] reported response rates ranging from 13% to 100% when treating cutaneous manifestations of cGVHD such as cutaneous sclerosis with rituximab.

In our study, we recorded a 43% overall response rate. One patient (7%) experienced CR. In general, treatment was well-tolerated with negligible toxicity. Similar to previous reports, the lowest response was seen in lungs. In fact, no improvement was seen in cGvHD of the lungs in any of these reports. Patients with lung involvement showed less impressive response rates ranging from 0% to 38%.[21,33,35,36] It is unknown if rituximab's reduced effectiveness in other organs apart from the skin is due to the treatment itself or if these organs are simply more susceptible to immune-related, irreversible cGVHD damage. Factors limiting the clinicians' ability to properly evaluate rituximab's effectiveness (or ineffectiveness) include the failure to utilise aggressive diagnostic tools when assessing organ damage prior to treatment, as well as a lack of objective clinical tools.

The rates of CR and treatment success observed in this study are slightly lower than reported for rituximab in the treatment of steroid-refractory cGVHD in previous studies.[19,21,33-38] However, time and response criteria in these studies varied or were not clearly defined, making it difficult to

directly compare results with our study. In these aforementioned studies, cGVHD was classified as both a limited and extensive disease and response criteria were not constant. This is why prospective and retrospective studies have reported different response rates and organ-specific responses. The NIH Consensus Development Project released new criteria for clinical trials involving this disease in order to create standard criteria for the diagnosis and response evaluation of cGVHD.[17,18] So far only a few studies have used these new NIH criteria. In this report we used the recently published NIH criteria for diagnosing of resistant ScGVHD and measuring response to rituximab. It is possible that the adoption of more stringent response measures has resulted in lower CR rates and cumulative response in this study. Furthermore, the participants in this study presented with severe cutaneous sclerosis and had been heavily pre-treated. The use of rituximab as a standard first-line therapy for cGVHD was examined in the Phase II prospective study by Malard et al with 83% overall response rate.[39] A similar overall response rate of 88% was noted by Solomon et al using calcineurin inhibitor and rituximab without CS.[40] It is possible that earlier intervention with anti-B-cell therapy could limit cGVHD-mediated irreversible organ damage.

To conclude, despite its small sample size, our study suggests that rituximab is safe to use as a salvage therapy when treating refractory ScGVHD. There is still an obvious need for better treatment for cutaneous sclerosis. Earlier intervention with rituximab therapy has the potential to limit irreversible cGVHD-related organ damage. Better-designed prospective studies are needed in order to determine the optimal timing, dosage and combinations rituximab or new generation of anti-CD20 agents in the treatment of cGVHD.

Conflicts of interest

The authors have no conflict of interests to disclose.

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