after 56 days, disease regression occurred. Ten days after the clinical response, grade I GvHD of oral mucosa developed for which no immunosuppressive treatment was given. Eighteen months after CSA withdrawal, the patient is still in complete remission and treatment-free.

Recently, two major immunotherapeutic interventions were attempted in six NHL patients who relapsed after BMT: the withdrawal of immunosuppressive therapy and, in due time, DLI. However, three of these cases achieved complete response after CSA or tacrolimus withdrawal without any further DLI. This finding and the result obtained in our patient indicate that discontinuation of immunosuppressive therapy may restore a GvNH effect also in indolent lymphoma, although the risk of GvHD may represent a major problem. Although spontaneous remission of low-grade NHL should also be taken into account, the temporal association of the clinical response with the CSA withdrawal indicates that the clinical response was likely to have been due to a GvNH effect.

Considering that the notable treatment-associated mortality of myeloablative regimens in NHL limits the benefit resulting from the GvNH effect and that myeloablative regimens are no longer mandatory in the preparation of allografting, the so-called mini-allograft may represent an alternative strategy to attained the beneficial effect of adoptive immune therapy.

Massimo Martino, Giuseppe Irrera, Giuseppe Messina, Giulia Pucci, Fortunato Morabito, Pasquale Iacopino
Centro Trapianti di Midollo Osseo e Terapia Sovramassimale Emato-Oncologica Alberto Neri, Dipartimento di Emato-Oncologia, Azienda Ospedaliera Bianchi-Melacrino-Morelli, Reggio Calabria, Italy

**Key words**

Graft-versus-tumor, low-grade lymphoma, allogeneic bone marrow transplantation, cyclosporin-A.

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**Correspondence**

M. Martino, M.D., Centro Trapianti di Midollo Osseo e Terapia Sovramassimale Emato-Oncologica, Dipartimento di Emato-Oncologia, Azienda Ospedaliera Bianchi-Melacrino-Morelli, 89100 Reggio Calabria, Italy. Phone: international +39-0965-27191 – Fax: international +39-0965-25082 – E-mail: morctmo@tin.it

**References**


**Rituximab for the treatment of type II mixed cryoglobulinemia**

Sir,

Rituximab is an anti-CD20 human-mouse chimeric monoclonal antibody that has been shown to be effective in the treatment of B-cell low-grade non-Hodgkin’s lymphoma (NHL). Type II cryoglobulinemia is an immunoglobulin mediated disease of B-lymphocytes that may theoretically benefit from CD20 targeted therapy.

DM, a 58-year old man, presented in October 1994 with purpura and joint pain. Laboratory studies showed serum total protein and immunoglobulin levels of 71 g/L and 12 g/L, respectively, a monoclonal IgM component, a rheumatoid factor level of 600 IU/mL, cryoglobulin positivity and a reduction in C4 level. Serum transaminases, serum creatinine, blood cell counts and urine analysis were normal. Serologic and genomic studies showed HCV
positivity (genome 1b). Bone marrow biopsy was negative for lymphoma.

Treatment with interferon-α-2b (IFN) 3 MIU three times a week for 6 months was ineffective. Subsequent treatments included intermediate doses of cyclophosphamide, prednisone, danazol and plasmapheresis, again without any detectable improvement.

By August 1998 the purpura and arthralgia had become much severe. Karnofsky’s performance status was 60. Lymph nodes, spleen and liver were not palpable. Bone marrow biopsy was still negative for lymphoma. The patient had a serum creatinine concentration of 22 mg/L, a glomerular filtration rate of 54 mL/min and proteinuria (2 g day). The hemoglobin level was decreased to 74 g/L. Total serum protein, immunoglobulin and monoclonal IgM levels were 63 g/L, 7 g/L and 2 g/L, respectively. Rheumatoid factor (RF) and C4 titers were 868 IU/mL and 8 mg/100 mL.

Rituximab was administered at a dose of 375 mg/m² iv every 7 days. No steroids, immunosuppressive or other cytotoxic agents were given. The patient tolerated the first two perfusions very well. Even before the second infusion of Rituximab a clinical improvement had become evident, there being less joint pain and purpura. However, the planned subsequent doses of rituximab were not given because the patient developed acute left-sided amaurosis with a documented thrombosis of the retinal arterial. No deficiency of protein S, protein C or antithrombin III was found. There was no resistance to activated protein C. Endocardial vegetations or atheromatous plaques of supra-aortic vessels were not found by ultrasound analysis. Treatment with rituximab was withdrawn and the patient was maintained on therapy with acetylsalicylic acid 100 mg/daily. Subsequently weekly observation of clinical status and laboratory data showed a progressive improvement of all signs of disease, with a nearly complete disappearance of purpura and arthralgia and a progressive reduction in the RF level down to 71 IU/mL (Figure 1). Total immunoglobulins, monoclonal IgM/k, C4, serum creatinine and urinary protein levels remained unchanged. This improvement lasted for three months, then the patient again started complaining of purpura and arthralgia. His RF level rose. The symptoms were mild and responded to low-dose prednisone.

Since the disease had been unresponsive to IFN and to cyclophosphamide and the patient had gained no benefit from steroids and plasmapheresis, and taking into account the poor general condition of the patient and the intensity of his symptoms, we believe that the response to rituximab was clinically significant.

Rituximab may hold promise for the treatment of type II cryoglobulinemia and other immunoglobulin-mediated diseases. We are not aware of other episodes of arterial or venous thrombosis related to the use of rituximab, but the retinal artery occlusion occurring in our patient is a warning to monitor the administration of rituximab to patients with abnormal plasma proteins very carefully.

Francesco Zaja, Domenico Russo, Giovanna Fuga, Francesca Patriarca, Anna Ermacora, Michele Baccarani
Chair and Division of Hematology, Department of Clinical and Morphological Research, University Hospital and School of Medicine, Udine, Italy

Key words
Type II mixed cryoglobulinemia, rituximab, immunoglobulin-mediated diseases.

Correspondence
Francesco Zaja, M.D., Clinica Ematologica, Policlinico Universitario, p.zza S. Maria della Misericordia, 33100 Udine, Italy. Phone: international +39-0432-559662 – Fax: international +39-0432-559661.

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