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### Complete molecular remission induced by rituximab in a patient with diffuse large cell lymphoma

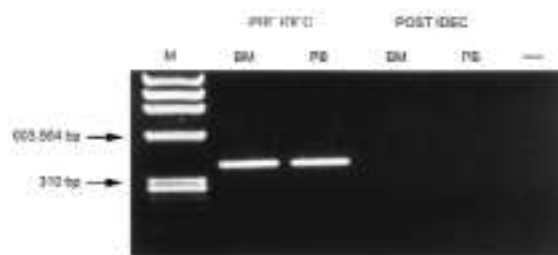
Along with the comprehensive data concerning our institutional experience on the use of rituximab for treatment of non-Hodgkin's lymphoma, we describe the first case of molecular remission induced by the chimeric anti-CD20 monoclonal antibody in a diffuse large cell lymphoma patient.

Sir,

The treatment recommendations for low-grade non-Hodgkin's lymphomas (LG-NHL) remain controversial to say the least and, unfortunately, the prognosis for these patients has not changed in more than 20 years.<sup>1</sup> Rituximab is a chimeric anti-CD20 monoclonal antibody containing human IgG1 and  $\kappa$  constant regions with murine variable regions.<sup>2</sup> The CD20 antigen is expressed consistently on nearly all human B-cells and most B-cell lymphomas present this antigen on the cell surface. Rituximab induces responses in around half of the patients with follicular LG-NHL<sup>3</sup> and has also demonstrated activity in intermediate-grade and high-grade NHL.<sup>4</sup>

We report here our institution's experience, in terms of clinical results, on the treatment of 12 patients with relapsed B-cell lymphoma. The patients, 8 males and 4 females, ranged from 35 to 68 years of age (median age: 50 years). Four patients had B symptoms. The distribution of the histologic subtypes was as follows: follicular lymphoma, 7 patients; small lymphocytic lymphoma, 3 patients; mantle cell lymphoma, 1 patient; and diffuse large cell lymphoma, 1 patient. Four patients had stage III disease according to the Ann Arbor staging system and 8 patients were in stage IV with bone marrow involvement. No patient had bulky disease. The patients had received a median of 3 prior, heterogeneous regimens (range 2-5). The median time from diagnosis was 3.5 years. All patients received 4-hour infusions of rituximab (375 mg/m<sup>2</sup>) once weekly for four doses over a period of 22 days.

Clonal IgH rearrangements were amplified by polymerase chain reaction starting from genomic DNA and using VH.L consensus primers and a JH.D primer as described elsewhere.<sup>5</sup> The sensitivity of detection of tumor cells ranged from 10<sup>-3</sup> to 10<sup>-5</sup>. Of the 12 patients, 4 (34%) achieved a complete response (CR)



**Figure 1.** Agarose gel showing samples from a patient with diffuse large cell lymphoma, amplified with patient-specific primers. Clonal product was seen only in pre-rituximab (IDEC) treatment samples. M: molecular weight marker; BM: bone marrow; PB: peripheral blood; —: negative control.

and 3 (25%) a partial response (PR) with an overall response rate (CR plus PR) of 59% (7/12). The median time to response was 45 days with continued improvement in response at 2 months. Of the stage IV patients with bone marrow involvement, 4/8 (50%) obtained a response (3 CR and 1 PR). Of the 7 follicular lymphoma patients, 3 (43%) achieved a CR and 2 (28.5%) a PR with a global response of 71.5%.

The patient with diffuse large-cell lymphoma achieved a molecular CR in addition to CR. He was given second-line treatment with an autologous bone marrow transplantation obtaining a good clinical PR with the persistence of molecular disease. Two months after rituximab treatment he showed a clinical CR and after 3 months molecular disease was no longer present in either peripheral blood or bone marrow (see Figure 1). At present, after 12 months this patient is still alive in CR. It is noteworthy that in this case the first CR had lasted only 4 months. This particular aspect is very interesting because it is the first evidence of a molecular disease negativity being obtained in diffuse large cell lymphoma by rituximab.

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#### Key words

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### A brief intensive chemotherapy in T-prolymphocytic leukemia

We report the case of a patient with T-prolymphocytic leukemia resistant to deoxycoformycin therapy. As second line therapy, brief, intensive chemotherapy, developed for Burkitt's lymphoma was administered achieving complete remission of the disease. As consolidation therapy, an autologous stem cell transplantation was performed. After a follow-up of 20 months the patient is disease-free.

Sir,

T-prolymphocytic leukemia (T-PLL) is a rare lymphoproliferative disease derived from mature, post-thymic T-lymphocytes, as demonstrated by immunophenotypic positivity for either CD4 or CD8, with the former being more often represented, and negativity for Tdt and CD1a.

The prognosis of this disease is considered bad, with poor response to traditional protocols of chemotherapy and a median survival of 7.5 months.<sup>1</sup>

We describe a case of a 53-year old male presented with hepato-splenomegaly, diffuse lymphadenopathy, lymphocytosis of  $120 \times 10^9/L$ , slight thrombocytopenia ( $130 \times 10^9/L$  platelets) and normal hemoglobin concentration (13.5 g/dL).

The immunophenotype defined a population of mature T-cells positive for CD3, CD4, CD5, CD7, TCR  $\gamma/\delta$ , and negative for Tdt, CD1a and CD25.

A diagnosis of the variant with small prolymphocytes of T-PLL was made and therapy with deoxycoformycin (DCF, 7 mg weekly) was started.<sup>1</sup> Because of the lack of response after five cycles, second line chemotherapy was instituted according to a protocol designed for Burkitt-like non-Hodgkin's lymphomas (NHL) (Codox M-Ivac: Codox M regimen: day 1: cyclophosphamide 800 mg/m<sup>2</sup>, vincristine 1.5 mg/m<sup>2</sup>, doxorubicin 40 mg/m<sup>2</sup>; days 2-5: cyclophosphamide 200 mg/m<sup>2</sup>; day 8: vincristine 1.5 mg/m<sup>2</sup>; day 10: methotrexate 1,440 mg/m<sup>2</sup>. Ivac regimen: days 1-5: etoposide 60 mg/m<sup>2</sup>, ifosfamide 1,500 mg/m<sup>2</sup>, mesna 360 mg/m<sup>2</sup>, 7 doses in 24 h; day 1 and 2: cytarabine 2 gm/m<sup>2</sup> for a total of 4 doses. After 2 cycles of combined chemotherapy with the Codox-M-Ivac regimen, complete clinical, morphologic and immunophenotypic remission was obtained and peripheral

blood stem cells were harvested after the last cycle of chemotherapy. High dose melphalan (140 mg/m<sup>2</sup>) and unfractionated total body irradiation (10 Gy) were administered followed by peripheral stem cell (PBSC) autograft.

This treatment was well tolerated with hematologic reconstitution by day +28 after PBSC infusion. After a follow-up of twenty months, the patient is disease free with normal hematologic and immunophenotypic parameters in the peripheral blood and bone marrow.

Recently, DCF, an inhibitor of adenosine deaminase, has been proposed as first line therapy in T-PLL.<sup>2</sup> However despite 5 cycles of this therapy, our patient showed limited response with recurrence of lymphadenopathy and lymphocytosis between the single cycles.

The choice of the Codox M- Ivac protocol was suggested by the high proliferation rate of the disease, the young age of the patient and the disappointing results reported in the literature with traditional combination chemotherapy.

The Codox-M-Ivac regimen was developed for treatment of Burkitt's or Burkitt-like NHL as brief, intensive chemotherapy, combining two non-cross-resistant protocols.<sup>3</sup>

As already suggested by some authors, this type of brief, intensive protocol may be an option for poor prognosis NHL.<sup>4</sup> The consolidation of the complete remission with autologous PBSC, although experimental, may be a reasonable means to avoid the early relapse frequently seen in T-PLL.<sup>5</sup>

In conclusion, this case illustrates the feasibility and efficacy of a brief intensive chemotherapy program in the management of T-PLL. The disease-free survival of over one year suggests that this is a possible therapeutic approach for younger patients affected by this rare lymphoproliferative disease with a very poor prognosis.

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### Key words

T-prolymphocytic leukemia, deoxycoformycin, autologous peripheral blood transplantation.

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