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CASE REPORT

Campath-1H in B-chronic lymphocytic leukemia: report on a patient treated thrice in a 3 year period

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Monoclonal antibody (mAb) therapy is a novel alternative treatment for lymphoid malignancies. In this report we present a 55-year-old patient with B-chronic lymphocytic leukemia, who was initially treated with chlorambucil p.o. and subsequently with cyclophosphamide iv with poor response. Then Campath-1H mAb was administered. He received three cycles of Campath-1H, over a 3 yr period, lasting 12 weeks each, at a final dose of 30 mg weekly, on an outpatient basis. After each cycle of Campath-1H administration there was a significant decrease of the size of the palpable lymph nodes, spleen and liver. Restoration of the blood lymphocyte count to normal and a significant decrease of the bone marrow lymphocytic infiltration was observed at the end of each cycle. Therefore, a major clinical response was obtained after all cycles. Campath-1H administration was well tolerated without causing any serious toxicity.
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Introduction

In B-chronic lymphocytic leukemia (B-CLL) complete response can be achieved with chemotherapy in a considerable number of patients.[1] However, complete eradication of the neoplastic clone cannot be elicited, and hence new forms of therapy are warranted. Among them mAbs have been used.[2] These antibodies are directed against antigenic epitopes on the surface of the cells and have much greater specificity for the malignant clone than the conventional chemotherapeutic agents. During the last few years the humanized Campath-1H antibody against the CD52w antigen of the lymphocyte surface became available for clinical studies, offering an alternative approach for the treatment of the B-CLL patients.[3] In this report we present a patient with B-CLL, who was successfully treated thrice with the Campath-1H mAb over a 3 yr period.

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Case report

Patient's history

A 55-year-old man was referred to us in April 1991 because of lymphocytosis (175×10^9/l), which was

accidentally discovered during a regular check up due to raised serum glucose levels. He had generalized lymphadenopathy [bilateral cervical (1×1 cm), axillary (2×2 cm) and inguinal (2×2 to 3×4 cm) lymph nodes] and mild hepatosplenomegaly (3 and 4 cms respectively). His blood count was as follows: Ht: 42.6%, Hb: 14.1 g/dl, WBC: 175×10^9/l (neutrophils: 1%, lymphocytes: 95%), PLT: 296×10^9/l. The diagnosis of CLL was confirmed by blood lymphocyte morphology, immunophenotypic findings (CD19/CD5 positive cells with low surface κ light chain expression), bone marrow examination (interstitial infiltration by lymphocytes $\approx$75%)[4] and lymph node biopsy (diffuse lymphocytic cell infiltration).[5] The clinical stage of our patient was Binet B,[6] as confirmed by a CT scan (slight hepatosplenomegaly and upper paraaortic lymph nodes smaller than 1.5 cm). He was placed on chlorambucil 10 mg/d p.o. for 10 d on a monthly basis.[7] A minor response to chlorambucil was observed, so that treatment was switched to cyclophosphamide iv (1 g/cycle, weekly) given for 8 consecutive weeks. Three months later, his disease was worsening with a lymphocyte increase (169×10^9/l), drop of Hb level (11.2 g/dl) and an increase of lymphadenopathy and splenomegaly. At this stage, he was placed on Campath-1H mAb.

Campath-1H treatment

The mAb became available in the context of a European Phase II Clinical Study of Campath-1H administration for B-CLL patients, failing conventional chemotherapy. The patient received three cycles of Campath-1H in a 3 y period. Each cycle lasted 12 weeks and Campath-1H was delivered thrice a week in 2 h iv infusion. The dosage of the mAb was escalated from 3 mg the first, to 10 mg the second and to 30 mg the third week and thereafter. Campath-1H was administered on an outpatient basis. He was closely observed for side effects in the Day Care Clinic for at least 10 h after every infusion course. The patient also received 1 g paracetamol and 1 mg dimethindene before each Campath infusion.

Treatment was well tolerated. There were no major allergic reactions. The side effects presented were fever and rigor during the first iv infusion, but these symptoms progressively decreased during the second and third treatment cycle.

Response to Campath-1H

The response was impressive: lymphadenopathy was dramatically decreased and a few axillary and inguinal nodes remained, not greater than 1 cm in diameter. Spleen and liver were not palpable after treatment (Figure 1). The WBC count became normal (Figure 2) and the CD19/CD5 positive clone was not detectable by flow cytometry in the blood after the last iv infusion of each cycle. The infiltration of the BM by lymphocytes was significantly decreased after each cycle (Figure 3). There was molecular evidence of residual disease in the blood as shown by PCR on DNA extracted from mononuclear cells, for the heavy chain gene rearrangement.

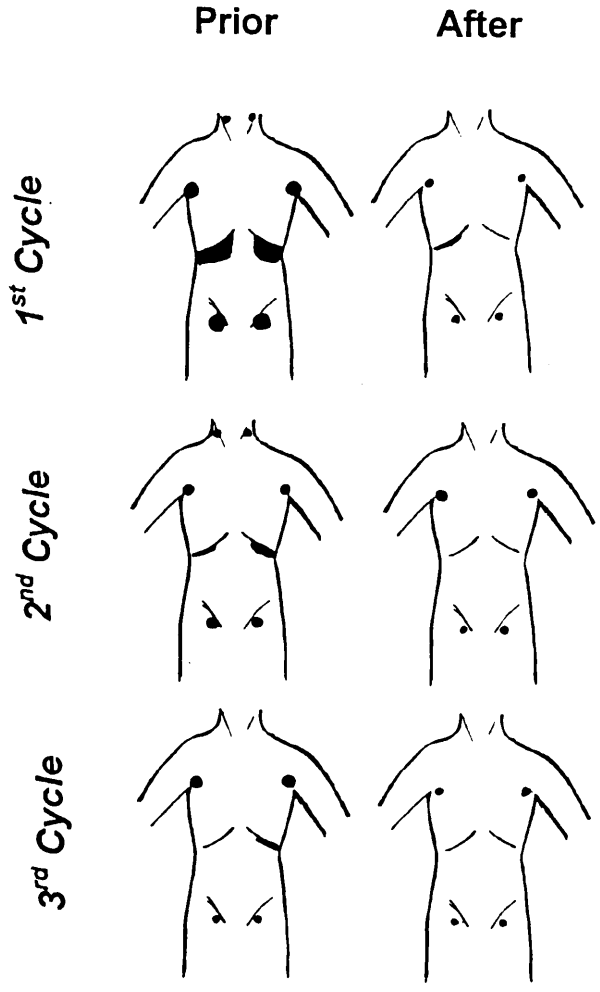

Figure 1 *Response of clinically palpable disease prior and after each cycle of Campath-1H administration.*

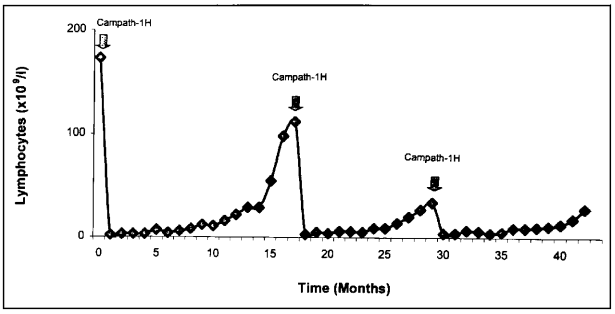

Figure 2 *Lymphocyte count in relation to Campath-1H administration.*

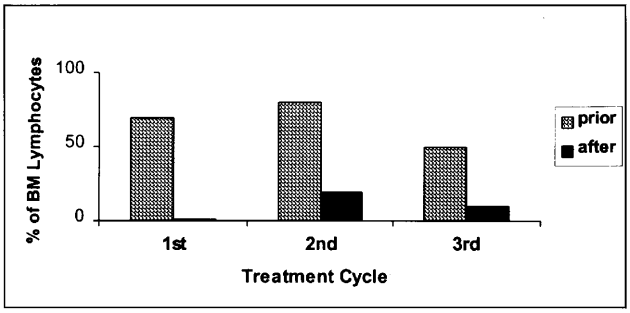

Figure 3 *Response of BM disease to Campath-1H administration.*

The patient remained in clinical complete response for 1 yr after the first cycle of Campath. However, the WBC count gradually increased (Figure 2) and at the end of the year the BM revealed 80% infiltration by lymphocytes (Figure 3). It was therefore decided for the patient to receive another 12-week cycle of Campath-1H. The results were similar, with a decrease of palpable disease and reduction of the WBC count (Figures 1 and 2), but there was residual disease in the BM with an infiltration of 20% (Figure 3), documented morphologically and immunophenotypically.

Ten months after the end of the second cycle, and because of the slow increase of tumor load, the patient received a third cycle of Campath-1H. At the end of the third cycle disease was again controlled as shown in figures 1, 2 and 3.

The unavailability of the antibody prevented us from treating our patient with a fourth cycle of Campath-1H.

According to the IWCLL and NCI criteria complete response was achieved after each cycle of therapy.[8,9]

Discussion

The treatment of B-CLL includes single agent chemotherapy (chlorambucil, cyclophosphamide and/or prednisone), combination chemotherapy, and more recently purine analogues.[1,10–12] Responses have been reported in up to 80%[1.7.10–12] without eradication of the disease, in terms of molecular remission. Another alternative is allogeneic bone marrow transplantation.[13] Campath-1H is a new therapeutic approach for B-CLL. In our patient, a major response was achieved by Campath-1H and this was successfully repeated three times during a 3 yr period.

Campath-1H is usually considered to be more active against the blood and BM than the lymph node disease, particularly when the latter is bulky[3,14,15] However, in this patient it was equally effective in decreasing the peripheral blood and BM lymphocytes, as well as the size of palpable lymph nodes and the spleen.

Toxicity was not a limiting factor. Actually, the side effects were of less intensity during the second and third cycle of therapy. No myelotoxicity or opportunistic infections were observed. Thus, Campath-1H treatment offered our patient an excellent life quality. There are studies reporting that Campath-1H is effective in achieving complete or partial responses both in previously untreated and refractory to conventional treatment B-CLL patients.[2,3,14,16,17] Further investigation with clinical trials on a larger number of patients are necessary to document whether Campath-1H should be used only in refractory disease or as a first line therapy. For the time being it appears that Campath-1H may eradicate minimal residual disease[18] and that it can also be used for the harvest of peripheral blood stem cells for autologous BM transplantation in B-CLL patients.[15]

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