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Alemtuzumab in the treatment of relapsed chronic lymphocytic leukaemia – a report of three cases

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Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia observed in Europe. The disease is usually characterised by a long clinical course, however when progression occurs, therapeutic possibilities are limited. Treatment is palliative and aimed at stabilisation of the disease rather than at achieving complete remission. In patients resistant to purine analogues prognosis is poor – approximately 40% of patients survive beyond 12 months, with a mean survival of about 8 months. Thus, there is a need for alternative therapeutic procedures, preferably containing agents with a different mode of action than previously used chemotherapy. Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen. This has proven to be an effective alternative in patients with active disease previously treated with alkylating agents and purine analogues. In our study alemtuzumab was administered to patients with many years' history of CLL who had previously receivedvarious other chemotherapeutic regimens. The patients were younger than the median age observed in this disease. Partial remission of the disease was achieved in 2 cases. One patient attained stabilization of the disease. Rapid elimination of CD19/CD5+ leukemic cells from peripheral blood and marrow was observed, however regression of enlarged lymph nodes followed at a much slower rate. The side effects included fever and chills during drug infusion, pancytopoenia and infections. Basing on previous reports and own observations, it seems that the introduction of alemtuzumab, a therapeutic agent with a different mode of action than conventional chemotherapy, offers hopes of improving the outcome of treatment of chronic lymphocytic leukaemia.

Alemtuzumab w leczeniu nawrotów przewlekłej białaczki limfatycznej – opis trzech przypadków

Przewlekła białaczka limfatyczna (PBL) jest w Europie najczęściej spotykaną białaczką u osób dorosłych. Schorzenie to ma zazwyczaj wieloletni przebieg kliniczny, jednak w przypadku wystąpienia progresji możliwości terapeutyczne są ograniczone. Leczenie ma charakter paliatywny i jest zazwyczaj ukierunkowane na uzyskanie stabilizacji choroby, a nie uzyskanie całkowitej remisji choroby. U chorych na CLL, opornych na leczenie analogami puryn, rokowanie jest złe, jedynie 40% przeżywa dłużej niż 12 miesięcy, a średni czas przeżycia wynosi ok. 8 miesięcy. Istnieje zatem potrzeba zastosowania u tych pacjentów alternatywnych procedur terapeutycznych, najlepiej z użyciem preparatów o innym, niż uprzednio stosowane cytostatyki, mechanizmie działania. Alemtuzumab (MabCampath) jest humanizowanym przeciwciałem, skierowanym przeciwko antygenowi CD52, obecnym m.in. na limfocytach B i T. W świetle dotychczas opublikowanych badań klinicznych lek ten okazał się skuteczną alternatywą, u chorych z aktywną chorobą, leczonych uprzednio lekami alkilującymi i analogami puryn. Przedstawiamy opis trzech pacjentów leczonych alemtuzumabem, z wieloletnim przebiegiem choroby, u których stosowano dotychczas liczne kursy cytostatyczne. Chorzy ci byli młodsi niż wynosi średnia wieku dla PBL. W dwóch przypadkach uzyskano częściową remisję choroby, a w jednym stabilizację choroby. We wszystkich przypadkach obserwowano szybką eliminację białaczkowych komórek CD19/CD5+ z krwi obwodowej i szpiku. Zmniejszanie się powiększonych węzłów chłonnych następowało znacznie wolniej. Najczęściej występujące działania niepożądane to gorączka i dreszcze podczas wlewu alemtuzumabu, pancytopenia oraz zakażenia. Na podstawie dotychczasowych publikacji oraz obserwacji własnych wydaje się, że wprowadzenie alemtuzumabu, preparatu o innym, niż konwencjonalne cytostatyki, mechanizmie działania przeciwnowotworowego, stwarza nadzieję poprawy wyników leczenia przewlekłej białaczki limfatycznej.

Key words: chronic lymphocytic leukemia, alemtuzumab
Słowa kluczowe: przewlekła białaczka limfatyczna, alemtuzumab

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Introduction

Chronic lymphocytic leukaemia (CLL) is a malignant disease in which morphologically mature lymphocytes accumulate in the blood, bone marrow and the lymphatic system. It accounts for 30% of all leukaemia cases. Its incidence in Europe ranges from 1.5 to 3.36 cases per 100.000. The disease usually affects elderly people, the mean age of patients being more than 65 years, however about 12% of patients are below 50 years of age. Therapeutic management of patients suffering from CLL depends on the stage of the disease and its activity. Conventional chemotherapy of CLL is based on alkylating agents, with or without steroids, as well as purine analogues (fludarabine, 2chlorodeoxyadenosine – 2CdA). The treatment has a palliative character and is aimed at stabilisation of the disease rather than at achieving complete remission [1].

Monoclonal antibodies form a new, promising group of therapeutic agents, and their use in the treatment of haematological malignancies is increasing. Alemtuzumab is a humanized monoclonal antibody directed against CD52 which is expressed, among others, on B and T lymphocytes. The alemtuzumab molecule triggers the mechanisms of cellular lysis by means of antibody-dependent and complement-dependent cell cytotoxicity. It also has a direct anti-proliferative effect on the malignant cells. In view of recently published clinical trials, the drug has proven to be an effective alternative in patients with active disease who had been previously treated with alkylating agents and purine analogues [2, 3].

This study presents three CLL patients (2 women and 1 man, aged 38, 52 and 53 years), in whom alemtuzumab was used for the treatment of a consecutive relapse. All the patients had been previously on cytostatic protocol, receiving among others, alkylating agents, anthracyclines and purine analogues. Two patients had been previously treated with rituximab. The indications for the use of anti-CD52 antibody included progression of the disease which had been refractory to the applied treatment. Alemtuzumab (MabCampath, Schering AG.) was administered intravenously at standard doses of 30 mg [3] times a week with an escalating dose of 3, 10 and 30 mg during the first week of treatment. Premedication included clemastin 2 mg i.v. and paracetamol 500 mg orally. We also instituted infection prophylaxis with acyclovir and cotrimoxazole.

Case reports

Patient 1 (M.W.) was diagnosed with B-cell chronic lymphocytic leukaemia in 1992 at the age of 57. She presented with enlarged lymph nodes and spleen. The leukocyte count was 29.5 G/l with 80% of mature lymphocytes in peripheral blood and hemoglobin was 9,89G/l. Rai stage III was established. Prior to alemtuzumab treatment, the patient was receiving chemotherapy for 8 years, first chlorambucil until 1999, and then, in view of increasing resistance, CHOP (cyclophosphamide, adriblastin, vincristine, prednisone) for 2 cycles, and next – purine analogues in combination as FND (fludarabine, mitoxantron, dexamethason) – altogether 3 cycles. Disease progression was observed after approx. 6 months and the patient received another, fourth cycle of FND. The treatment resulted in the reduction of leukocytosis, and the disease manifested itself mainly in the form of abdominal lymphadenopathy (progression of the enlargement of subfascial and mesenteric lymph nodes which formed clusters in the hilus of the liver sized 4.5 cm x 2.6 cm and in the caudal region of the superior mesenteric vein – 8 x 3.3 cm) (Figure 1). In mid-November 2001 we decided to introduce alemtuzumab therapy. MabCampath was administered for 5 weeks at due doses, after which the

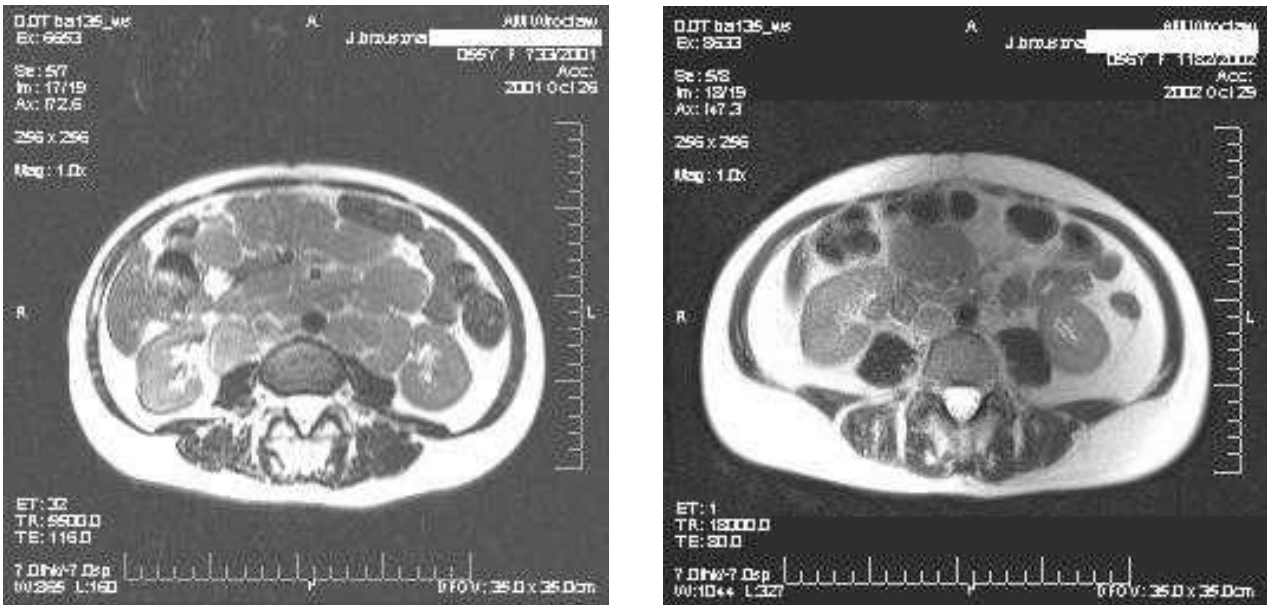

Figure 1. Patient 1. MRI of abdomen. Partial regression of lymph nodes after alemtuzumab therapy

treatment was discontinued due to agranulocytosis (L-0.3 G/l) and pneumonia. The patient was treated with antibiotics and granulocyte-colony stimulating factor (G-CSF) and when the symptoms of pneumonia subsided, she also received immunoglobulins. This resulted in the increase of leukocyte count, regression of pulmonary lesions; granulocytosis predominated in the bone marrow and peripheral blood and bone marrow did not reveal the presence of CD5/CD19+ cell populations. The patient remains untreated. A year and a half after the termination of alemtuzumab therapy, the leukocyte count remains below 5.0 G/l and the presence of CD5/CD19 cells in peripheral blood and bone marrow appears to be below 1%. Control abdominal MRI revealed the presence of a solitary cluster of lymph nodes (Figure 1).

Patient 2. E.M. aged 38. Stage II of CLL according to Rai, was diagnosed in 1997. The patient presented with increased peripheral lymphadenopathy of all groups and splenomegaly; bone marrow contained 80% lymphocytes. The leukocyte count in peripheral blood was 26 G/l with 70% of CD19/CD5+ lymphocytes. The patient received CVP (cyclophosphamide, vinblastine, prednisone), CHOP and next, in view of poor response, she received 6 cycles of FND, which provided stabilisation for 18 months. B symptoms (fever, sweating) and enlarged peripheral lymph nodes were the reasons for instituting methylprednisolone and, next, rituximab treatment, after which the disease stabilized for the next 4 months. The indications for alemtuzumab therapy included progression of the disease manifested by persistent lympadenopathy, especially on the neck and in the inguinal region, as well as in the abdominal cavity. Bone marrow contained 85% of CD19/CD5+ and CD23+ lymphocytes. Alemtuzumab treatment lasted from March to May 2002. In the third week of treatment a 50% regression of cervical and inguinal lymph nodes was noted. In the fourth week the patient developed neutropenia of 0.5 G/l and anaemia requiring substitution. During the first two weeks of therapy fever was observed on the day of infusion. Six weeks after termination of therapy the patient developed progressive disease with recurrent peripheral and abdominal lymphadenopathy which led to her death.

Patient 3. Z.N. aged 53. The diagnosis of CLL was established in 1998 on the basis of the findings of leukocytosis 118.6 G/l with 94% of CD19/5+, CD 20+ and CD 23+ lymphocytes. No anaemia or thrombocytopenia was found. The bone marrow contained 83.2% of lymphocytes. Physical examination revealed peripheral generalized lymphadenopathy, splenomegaly and enlarged retroperitoneal lymph nodes on ultrasound imaging. Rai II stage was diagnosed. The patient was treated with chlorambucil, which led to a decrease in leukocyte count to 50 G/l. In June 1999 leukocytosis increased to 80.0 G/l with 96% lymphocytosis and nodular progression – the patient received three 5-day 2CdA cycles, after which the leukocyte count fell to 26.0 G/l. In November 1999 the leukocyte count increased to 59.4 G/l, nodular progression set in and the patient was administered 2 CMC (cyclophosphamide, mitoxantron, 2CdA) cycles. The treatment was complicated with transient thrombocytopenia. Stabilization of the disease was achieved for the next 8 months and the leukocyte count remained at a level of 14 G/l. However, in October 2000, the disease progressed again with increased leukocytosis (53.2 G/l) and enlargement of peripheral lymph nodes. The patient was administered 3 cycles of FC (fludarabine, cyclophosphamide). The leukocyte count fell to 6 G/l, however severe thrombocytopenia complicated the course of treatment. The disease remained stabilized for 7 months after treatment after which it relapsed in August 2001, however purine analogues were not administered due to accompanying thrombocytopenia. The patient received

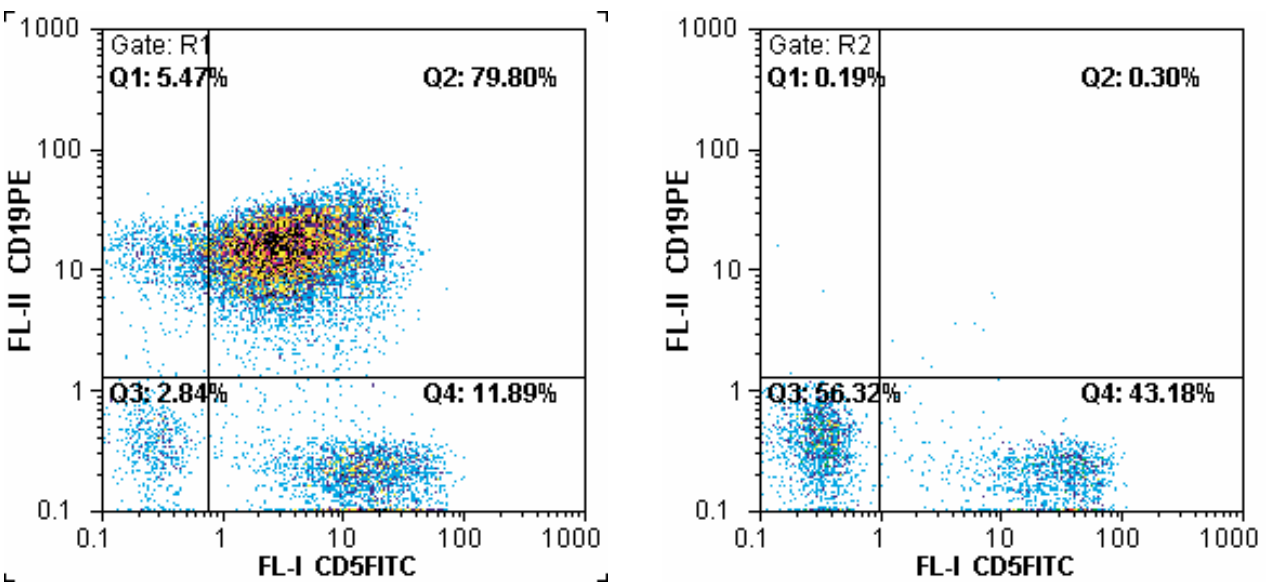

Figure 2. Flow cytometry of peripheral blood. Elimination of the CD19/CD5 (+) population after alemtuzumab therapy in patient 2

3 courses of COP (cyclophosphamid, vincristin, prednisone) + rituximab, followed by 4 courses of CHOP. Alemtuzumab treatment was instituted in April 2002. During the first infusion the patient developed chills and pyrexia of 40° C, as well as symptoms of bronchospasm. In the first three weeks of therapy the leukocyte count fell from 67.3 G/l to 1.6 G/l. The treatment was discontinued for about 4 weeks, after which the leukocyte count increased again to 20 G/l. In May 2002 the patient was administered alemtuzumab for 3 weeks resulting in the reduction of leukocytosis which lasted until September 2002, when it increased again to 31.5 G/l. He then received antiCD52 antibodies. After 3 months' stabilization the disease progressed rapidly with increasing leukocytosis, in consequence leading to the death of the patient.

Discussion

Chronic lymphocytic leukaemia is the most common adult leukaemia occurring in Europe. The disease is usually characterised by a long clinical course, however when progression occurs, the therapeutic possibilities are limited. In patients with CLL who are resistant to purine analogues the prognosis is poor – approximately 40% of patients survive beyond 12 months, with a mean survival of about 8 months [4]. Thus, there is need for alternative therapeutic procedures, preferably containing agents with a different mode of action than previously used chemotherapy. One of the options includes the use of monoclonal antibodies. Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen. High expression of the antigen (500 000 receptors on one cell) was found in 95% of normal and malignant B and T lymphocytes and – to a lesser degree – on monocytes, macrophages and eosinophilic granulocytes. The CD52 antigen is not present on the CD34 positive stem cells of the hematopoietic system [5]. The beneficial effect of almetuzumab therapy in patients with CLL resistant to previous chemotherapy was confirmed in multicentre studies. The response (CR + PR) accounts for 30% [2, 3, 6].

In our study alemtuzumab was administered to patients with many years' history of CLL who had previously received numerous chemotherapeutic regimens, including alkylating agents and purine analogues. The patients were younger than the median age observed in this disease. Partial remission of the disease was achieved in 2 cases despite the fact that the patients were in a consecutive relapse, however one patient developed progression of the disease after sic weeks and died. One patient attained stabilization of the disease. Consistently to data in literature, we observed rapid elimination of CD19/CD5 leukemic cells from peripheral blood and marrow, however regression of enlarged lymph nodes followed at a much slower rate [7-9]. Side effects included fever and chills during the alemtuzumab infusions, pancytopenia and infections. The infections were caused by profound immunosuppression associated with the primary disease (deficiency of antibodies) as well as with lymphopenia resulting from the elimination of CD 52+ cells from the peripheral blood. There were no cytomegalovirus reactivations. In the case of one patient (M.W.) pneumonia appearing in the course of leukopenia resulted in discontinuation of therapy. Despite this complication, the patient remains in partial remission lasting 18 months. It is worth noting that in this case the administration of alemtuzumab followed immediately after fludarabine treatment in the form of FND. According to Kennedy et al. the combination of anti-CD52 antibody with fludarabine is effective in refractory CLL, also in patients in whom the above mentioned agents were used as monotherapy [10]. Severe pancytopenia and infectious complications in the first two cases were the reason to modify alemtuzumab doses in the third patient. In this patient the treatment was aimed leukocyte count stabilisation and thus, when it was achieved, the treatment was discontinued until the increase of the white blood count reappeared. Despite the fact that the CD52 antigen does not occur on hematopoiesis stem cells, erythrocyte and platelet substitution was mandatory in all the cases. In two cases alemtuzumab treatment was administered to patients who previously received anti-CD20 monoclonal antibody (rituximab). According to Keating et al., alemtuzumab may also be effective in CLL patients who were resistant to rituximab [2]. On the basis of previous reports and own observations it seems that the introduction of alemtuzumab, a therapeutic agent with a different mode of action than conventional chemotherapy, offers hopes of improving the outcome of treatment of chromic lymphocytic leukaemia. At present, clinical studies are led on the use of alemtuzumab as first-line treatment of CLL [8]. However, the placement of alemtuzumab in CLL therapeutic protocols (first line treatment or salvage treatment, monotherapy or combined therapy?), as well as the determination of optimum dosage require further investigations.

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