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Case Report

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Imatinib therapy of Ph positive acute lymphoblastic leukaemia – 2 case reports

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Summary

Aim

The aim of this works is the presentation of two cases of relapsed Ph positive acute lymphoblastic leukaemia (ALL) to which the tyrosine inhibitor Imatinib (Glivec, Novartis) was applied. This therapy was earlier shown to be very helpful in the treatment of chronic myeloid leukemia.

Case discription

Case 1: A 17 year old patient with Ph positive T-ALL relapsed after allogenic transplantation of marrow and was treated with Imatinib in escalating doses from 200 to 600 mg per day. After 4 weeks of treatment the blastosis in the marrow had fallen from 96% to 7%. Blasts disappeared from the cerebrospinal fluid. At the same time, progression of hepatic and renal failure related to GVHD was observed. Imatinib withdrawal resulted in relapse, uncontrolled proliferation and the death of the patient.

Results

Case 2: Imatinib was used in the case of a 45 year old patient with Ph positive null-ALL and a mediastinal tumour. After autologous bone marrow transplantation, Imatinib therapy was begun for maintenance.. Daily doses of the drug amounted to only 200 mg owing to associated gastric complaints. After two months of therapy, an increase in blast cells in the bone marrow to 18% was noted. FLAM chemotherapy was given and complete haematological remission was achieved.

Conclusions

The cases described illustrate new possibilities in the treatment of Ph positive ALL. It is necessary, however, to conduct clinical trials in larger group of patients for the purposes of establishing optimal dosing, the most suitable phase of the disease in which to begin therapy and possible combinations with chemotherapy.

Key words **Ph positive acute lymphoblastic leukaemia • Imatinib**

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BACKGROUND

The Philadelphia chromosome (Ph) is the most frequently identified genetic factor in adult patients with acute lymphoblastic leukaemia (ALL). The frequency with which the chromosome is identified in this group of patients is estimated at between 20 and 40% [1]. Formation of the Ph chromosome is the result of a translocation between chromosomes 9 and 22 {t(9;22)(q34; q11)} which leads to the formation of the oncogene *BCR-ABL*. Transcription of the oncogene in ALL produces an mRNA molecule, of mass 7.5 kb, codes for a 190 kD protein (p-190). This process is the same as in chronic myeloid leukemia in which an mRNA molecule, of mass 8.5 kb, which codes for a 210 kD protein (p-210). The protein p-210 is the result of combining exons 2 of the ABL gene with exons 2 or 3 of the BCR gene (M-bcr region) (b2a2 and b3a2). Similarly p-190 results from the addition of exons 2 of the ABL gene to intron 1 of the BCR gene (m-bcr region) (ela2). The GMALL study (German Multicenter Trials of Adult ALL) showed that 77% of Ph positive ALL patients had the p-190 protein and 20% had the p-210 protein. 3% were found to have both proteins [1]. Fused proteins have several domains, among the most important of which are those which show tyrosine kinase activity, involved in the inhibition of apoptosis and in the stimulation of tumour growth [2]. Ph positive ALL, almost exclusively, has immunological characteristics in common with pre-B [3]. In a significant number of cases, leukaemia cells show expression of myeloid antigens. For example, within the LALA study group (Leucémie Aiguë Lymphoblastique de l'Adulte) CD34 was demonstrated in 89%, CD13 in 20% and CD33 in 15% [4].

The prognosis for Ph positive ALL is decidedly poor; patients with this diagnosis are included in the very high risk (VHR) group. The frequency of complete remission (CR) in these groups reaches almost 70% compared to around 85% in groups of Ph negative patients with ALL. Five year survival is less than 20% in comparison to around 48% in groups of patients with 'standard' risk. Survival time increases by 30–35% after allogenic marrow transplantation in the first CR [1,3]. New treatment possibilities appeared for patients with Ph positive ALL with the introduction of imatinib (STI571, Glivec, Novartis). This drug is a tyrosine kinase inhibitor and is unusually effective in cases of chronic myelogenous leukaemia (CML). It is possible to attain 95% complete haematological remission (CHR), 60% major cytogenetic response (MCR) and 41% complete cytogenetic remission (CCR) [5]. Further improvements in results can be attained by adding imatinib to chemotherapy, such as cytarabine [5]. The effectiveness of this drug in Ph positive ALL has not yet been fully described.

We present 2 cases of Ph positive ALL in which Imatinib was applied.

DESCRIPTION OF CASES

Case 1

A diagnosis of Ph positive pre-T cell ALL was made in the case of a 17 year old patient on the 26th of June, 2002. The results of additional tests are included in Table 1. The patient achieved CR thanks to application of EVAP therapy (epirubicin, vincristine, kidrolase, prednisone) according to the PALG (Polish Adult Leukemia Group) method. The course of treatment is illustrated in Table 2. Neurological symptoms arising during the period of remission consolidating chemotherapy (n. VII paralysis, epilepsy) were, to begin with, without change in the cerebrospinal fluid. Later, however, pleocytosis was observed (41/µl). Thanks to the application of cytostatic drugs and irradiation of the skull and spinal column, reversal of the neurological changes was achieved with normalization in the cerebrospinal fluid picture. On the 31st of December, 2002, an allogenic bone marrow transplantation was performed, the marrow having been obtained from a sister with suitable antigens. Unfortunately, on the 21st of March, 2003, recurrence of the disease was observed. Apart from infiltrating leukaemic marrow and blood cells, changes found in the cerebrospinal fluid included pleocytosis (350/µl). In the presence of increasingly serious symptoms of GVHD, (skin changes, diarhhoea, damage to the liver and kidneys) chemotherapy was halted and imatinib treatment was begun. The dose of the drug amounted to between 200 and 600 mg and was dependent on the count of leucocytes and thrombocytes. Tests carried out after 4 weeks of treatment showed a reduction in the proportion of blast cells in the marrow from 96% to 7% and, interestingly, a normalisation in the morphological picture in the cerebro-spinal fluid. After 2 further weeks, the symptoms of liver damage (bilirubin 4.5 mg%) and kidney damage (creatinine 4.2 mg%, urea 178 mg%) were so much more evident that it was decided to pause imatinib treatment. The break in treatment brought about uncontrolled proliferation during the following 2 weeks, culminating in the death of the patient on the 13th of May 2003.

Case 2

A 45 year old patient was diagnosed with Ph positive null-cell ALL on the 8th of October, 2002. Additional test results and the course of treatment used are described in Tables 1 and 2. On the 10th of November, following application of the EVAP scheme, CR was achieved. However, marrow tests performed after remission consolidating treatment showed an increase in the percentage of blast cells to 8%. FLAM treatment was applied (fludarabine, cytarabine, mitoxantrone) and resulted in a return to complete remission. Owing to the lack of a source of marrow within the family for an allogenic transplant, it was decided to carry out and autologous transplant. After completing haemopoietic reconstruction Imatinib treatment was begun. A small dose was used – 200 mg/day, owing to strong gastric disturbances (stomach pain, nausea, vomiting). After 2 months of treatment, tests on the marrow showed an increase in the count of blast cells to 18%. It was decided that intensive FLAM therapy should be used, which again resulted in CR and, having identified a suitable non-related donor, the patient was admitted to the Marrow Transplantation Department in Wrocław where, unfortunately, the patient died following a further replase in September 2003.

DISCUSSION

The presented cases illustrate new possibilities in the treatment of Ph positive ALL. Imatinib, which is unusually effective in the treatment of CML, was very quickly applied to diseases characterised by this same type of genetic change.

Table 1. Description of patients with Ph positive ALL, treated with imatinib: Clinical picture at the time of diagnosis.

	M, 17 years	F, 45 years
Date of diagnosis	24-06-2002	08-11-2002
Type of Leukaemia	**pre-T** CD19- HLADR- cCD3+(84%)TdT+(79%) CD7+(83%)CD5(88%) CD2 (95%) MDR-	**null-cell** CD19-HLADR+(83%) CD3-TdT+(22%) CD34+(51%)CD13-CD33- MDR-
Additional clinical details	lymphadenopathy (till 2 cm)	breast tumour
Blood morphology	Hb 14.6 g% RBC 4.75 T/l PLT 66 G/l WBC 132 G/l blasts 75%	Hb 12.1g% RBC 3.59 T/l PLT 195 G/l WBC 145 G/l blasts 70%
Myelogram	89% cells with morphology of small lymphoblasts	90% cells with morphology of small lymphoblasts
Genetic findings	BCR/ABL + (30% cells, FISH)	BCR/ABL+ (22% cells, FISH)

Table 2. Patients with Ph positive ALL: course of treatment.

	M, 17 years	F, 45 years
Treatment type (commencement date)	**EVAP according to PALG** (26-06-2002)	**EVAP according to PALG** (08-11-2002)
Result of treatment (date)	CR (13-08-2002)	CR (10-12-2002)
Post-remission treatment	Consolidation (PALG) Treatment of meningeal leukaemia, which appeared in the consolidation phase, first with neurological symptoms (n. VII paralysis, epilepsy), and later, changes in the cerebrospinal fluid – irradiation, cytostatics AlloBMT (31-12-2002) Relapse: 21-03-2003 IMATINIB - 6 week treatment with doses between 200 and 600 mg; after 4 weeks there was a reduction in blasts in the marrow from 96% to 7% and in the CSF from 350 to 3/ul - treatment halted owing to liver and kidney damage (GVHD) Death: 13.05.2003	Consolidation (PALG) 8% blasts in marrow – **FLAM** **AutoPBPCT (01-04-2003)** IMATINIB – 2 month treatment with doses between 200 and 400 mg (owing to stomach pain, nausea, vomiting) Relapse (blasts 18%) FLAM Death: 09.2003

The discovery of the great effectiveness of the drug was first shown in individual cases of resistant and relapsing Ph positive ALL [6–9], and later in a clinical trial on a larger group of patients. Ottmann et al. [10], working with a group of 56 patients with resistant and relapsing Ph positive ALL, achieved CR in 29% of cases. The elementary loss of sensitivity to imatinib and recurrence of disease is connected with resistance mechanisms such as: increased gene expression, amplification and point mutations, and also increased expression of multidrug resistance genes (MDR) [11]. An effective means of breaking the resistance of leukaemia cells is the combination of imatinib with chemotherapy. Thomas et al. [12] used the drug in association with a hyper-CVAD scheme on a group of 20 patients with newly diagnosed Ph positive ALL, achieving CR in all cases; 9 out of 10 patients who underwent further alloBMT attained a status of CR for an average 12 months, the other 10 patients in the group averaged 20 months in CR. Imatinib shows great value in the preparation of Ph positive ALL patients for alloBMT by bringing them to haematological and molecular remission, by elimination of residual BCR-ABL positive disease [13]. The obvious therapeutic possibilities of imatinib may give justification for autologous transplants in patients who have no alloBMT donors [14].

The cases we present are very interesting from the point of view of casuistry of the Philadelphia chromosome in pre-T and null cell ALL. In the first patient, imatinib was used in early relapse after alloBMT, together with CUN, and strong symptoms of GVHD led to an accumulation of toxic symptoms. Nevertheless, a reduction in the count of blast cells in the marrow was seen, from 96% to 7% and, interestingly, in the cerebrospinal fluid from 350 to 3 in 1 µl. In the second case an attempt was made to eliminate residual disease after autologous transplantation of marrow cells. One of the causes for the lack of response was the use of a reduced dosage of the drug (200 mg), because of gastric distress, which has been reported in the majority of patients (70%) during imatinib treatment [3]. Complete remission was achieved after chemotherapy.

In our opinion imatinib is of the highest value in the treatment of Ph positive ALL when combined with chemotherapy and in the preparation of patients for transplantation of marrow, probably including autologous transplantation. The fixing of optimal dosing, in relation to the composition of chemotherapy and phases of disease in which the drug should be used, demands clinical trials in a larger group of patients.

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