

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA WITH POSITIVE PHILADELPHIA CHROMOSOME, INDICATION FOR BONE MARROW TRANSPLANTATION AND ALTERNATIVE THERAPY

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SUMMARY:

Introduction. Biomolecular anomalies have a definite prognostic significance in acute lymphoblastic leukemia in childhood. From all of these, of great impact is the Philadelphia chromosome (t (9, 22)) with BCR1-ABL fusion product. **Objectives.** Taking into consideration the clinical and biological characteristics of our patients, we aimed to analyze their evolution after treatment performed in conformity with current standards. **Materials and methods.** The retrospective study was performed on 104 cases of children diagnosed and treated for LAL in III-rd Paediatric Clinic Timișoara during 2000-2008. All patients were investigated in terms of molecular cytogenetic. **Results.** In our study group Philadelphia chromosome (BCR1-ABL positive) was detected in 8 cases (5 at onset and 3 at relapse diagnosis). In 6 of the 8 cases the age of onset was over 6 years. Regarding white blood cell number at disease onset, it was below 20×10^3 in 2 cases and above 100×10^3 in 2 cases. CNS (Center Nervous System) impairment was not present at disease onset, but it was still diagnosed in relapse for one case. Response to treatment with prednisone was good in 4 cases, and response to induction therapy was favorable in 3 cases. 4 patients were treated with imatinib mesylate and allogeneic hematopoietic stem cell transplantation was performed in 2 cases. 4 patients died during or after conventional treatment due to infectious complications. In another case death occurs due to a systemic infection with herpes simplex virus after allogeneic transplantation from an unrelated donor. Recurrent disease was the cause of death in one case. **Conclusions.** Although cases of Philadelphia chromosome positive acute lymphoblastic leukemia, are rare in childhood, they require special attention in terms of correct and complete diagnosis establishment (immunophenotype, karyotype, molecular biology) and appropriate treatment in order to increase long-term survival. Beside conventional treatments, these patients benefit from bone marrow transplantation and specific treatment with tyrosine-kinase inhibitors, the latter being able to improve in a significantly way life expectancy of these patients.

Key Words: Philadelphia chromosome, acute lymphoblastic leukemia, bone marrow transplantation, Imatinib

LEUCEMIILE ACUTE LIMFOBLASTICE (LAL) CU CROMOZOM PH+ LA COPIL, INDICAȚIE DE TRANSPLANT MEDULAR ȘI TERAPIE ALTERNATIVĂ

Rezumat:

Introducere. Anomaliile biomoleculare au o semnificație prognostică certă în leucemiile acute limfoblastice la copil, din rândul lor desprinzându-se prin impact cromozomul Philadelphia (t(9;22)) cu produsul de fuziune BCR1-ABL. **Obiective.** Având în vedere caracteristicile clinice-biologice ale pacienților noștri, ne-am propus să analizăm evoluția acestora în condițiile efectuării tratamentului conform standardelor actuale. **Material și metodă.** Am urmărit retrospectiv 104 cazuri de copii cu LAL diagnosticați și tratați în Clinica III Pediatrie Timișoara în perioada 2000-2008, care au fost investigați din punct de vedere citogenetic molecular.

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Rezumat (continuare): Rezultate. Din 104 cazuri cu LAL am decelat 8 cazuri cu cromozom Philadelphia pozitiv (BCR1-ABL pozitiv). În 6 din cele 8 cazuri vârsta la debut a fost peste 6 ani. În ceea ce privește numărul de leucocite, acesta a fost sub 20×10^3 în 2 cazuri și peste 100×10^3 în 2 cazuri. Afectarea SNC nu a fost prezentă la debut în nici unul din cazuri, ea fiind totuși diagnosticată la recidivă într-un caz. Răspunsul la tratamentul cu prednison a fost bun în 4 cazuri, iar răspunsul la terapia de inducție a fost favorabil în 3 cazuri. 4 pacienți au urmat tratament cu Imatinib, iar transplantul alogenic de celule stem hematopoietice s-a efectuat în 2 cazuri. 4 pacienți au decedat în timpul sau după terminarea tratamentului convențional prin complicații infecțioase. Într-un alt caz decesul a survenit secundar unei infecții sistemice cu herpes virus după transplantul alogenic de la donator neînrudit. Boala recidivată a fost cauză de deces într-un caz. Concluzii. Deși cazurile de leucemie acută limfoblastică cromozom Philadelphia pozitive sunt rare la copil, ele necesită o atenție deosebită în ceea ce privește diagnosticul complet (imunofenotip, cariotip, biologie moleculară) și încadrarea terapeutică adecvată în scopul creșterii supraviețuirii pe termen lung. Alături de tratamentul convențional, acești pacienți beneficiază de transplant medular și de tratament specific cu inhibitori de tirozin-kinază, acesta din urmă fiind în măsură să le amelioreze semnificativ speranța de viață.

INTRODUCTION

Some years ago prognostic factors for children with acute lymphoblastic leukemia (ALL) were age, sex, white blood cells count at onset, FAB type, karyotype, immunophenotype, recently study groups give special importance to treatment response, biomolecular and genetic abnormalities [1]. Through genetic alterations associated with high-risk disease and unfavorable evolution, t(9; 22)/Philadelphia chromosome (Ph cr) and t(4; 11) occupy an important place. These genetic abnormalities are criteria that establish the classification of patients in the high-risk group (HR).

Statistical data reveals that Ph cr is positive in 3-5% of childhood ALL and in about 20% of the adult ALL [1]. This translocation causes rearrangements of ABL proto-oncogene (chromosome 9) and BCR gene (chromosome 22), resulting in a fusion product with altered tyrosine kinase activity [2]. The presence of Ph cr and BCR1-ABL fusion gene can be highlighted by

molecular cytogenetic techniques (RT-PCR - reverse transcription- polymerase chain reaction and FISH - fluorescence in situ hybridization). Conventional techniques do not detect the translocation in the vast majority of cases [5].

Clinically, the presence of Ph cr is associated with poor response to conventional therapy and unfavorable prognosis, with reduced rate (20-30%) of long-term survival (5 years) [3]. The combination of the two unfavorable prognostic factors such as Ph cr and resistance to corticotherapy is associated with even lower survival rates [4]. For these patients hematopoietic stem cell transplantation (HSCT) and treatment with tyrosine kinase inhibitors offer the chance to get improved survival rates [4,3]. Still, some groups of patients with certain clinical and biological characteristics (age at onset between 1 to 9 years, small number of leukocytes (WBC) in diagnosis, good response to corticotherapy and induction remission treatment) can be cured with conventional treatment [1].

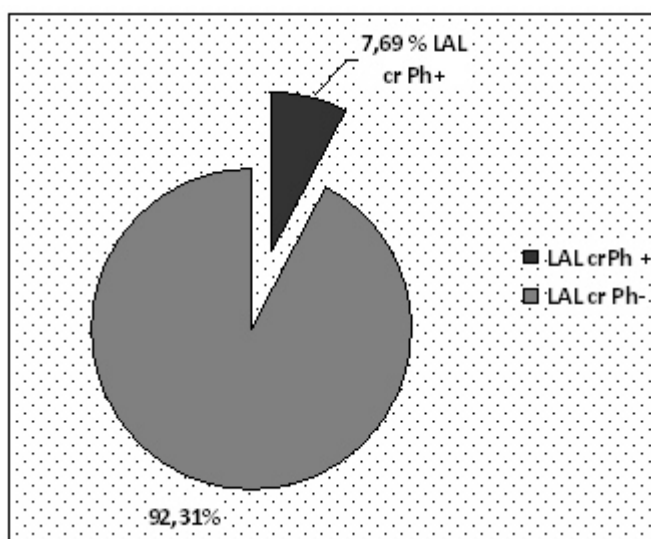


Fig. 1 Childhood Ph cr positive ALL frequency
Cr Ph+ ALL frequency

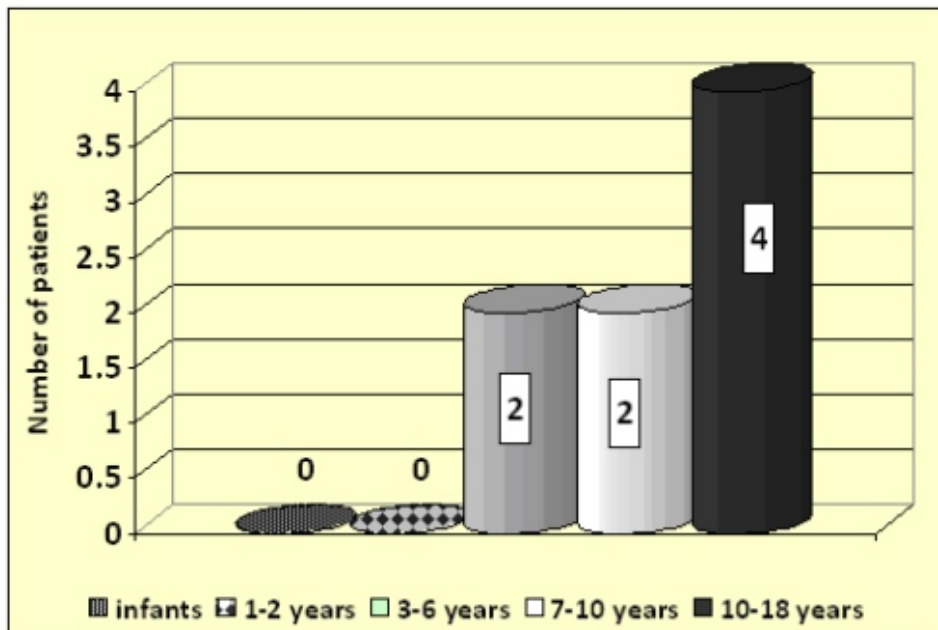


Fig. 2 Age group distribution in Ph+cr ALL

PATIENTS AND METHOD

We retrospectively analyzed a total of 104 patients under 18 years diagnosed and treated for ALL in the III-rd Paediatric Clinic Timisoara over a 9 years period between 2000 and 2008. Complete diagnosis was based on the following investigations: morphocytochemical study of atypical blast (FAB), immunophenotype, conventional cytogenetic (karyotype) and molecular (FISH, RT-PCR) studies. We analyzed clinical and biological characteristics and evolution of patients with Ph cr positive ALL at initial diagnosis or in disease relapse. The treatment was performed in conformity with current standards in all cases.

RESULTS

Ph cr was demonstrated in 5 cases at disease onset, representing 4.8% of ALL cases (Figure No. 1). In 3 cases, cr Ph was detected at the disease relapse. In these last cases the cytogenetic examination was not performed at disease onset.

The sex ratio for the Ph cr positive patients was 5:3 in favor of female gender. Taking into consideration the age at onset, most cases belonged to the 6-18 years age group. (Figure No. 2). FAB morphologic classification was L1 in 4 cases, L2 in 4 cases. WBC at onset was below $20 \times 10^3/l$ in 25% of cases, between $20-100 \times 10^3/l$ in 50% of cases and in other cases it was above $100 \times 10^3/l$.

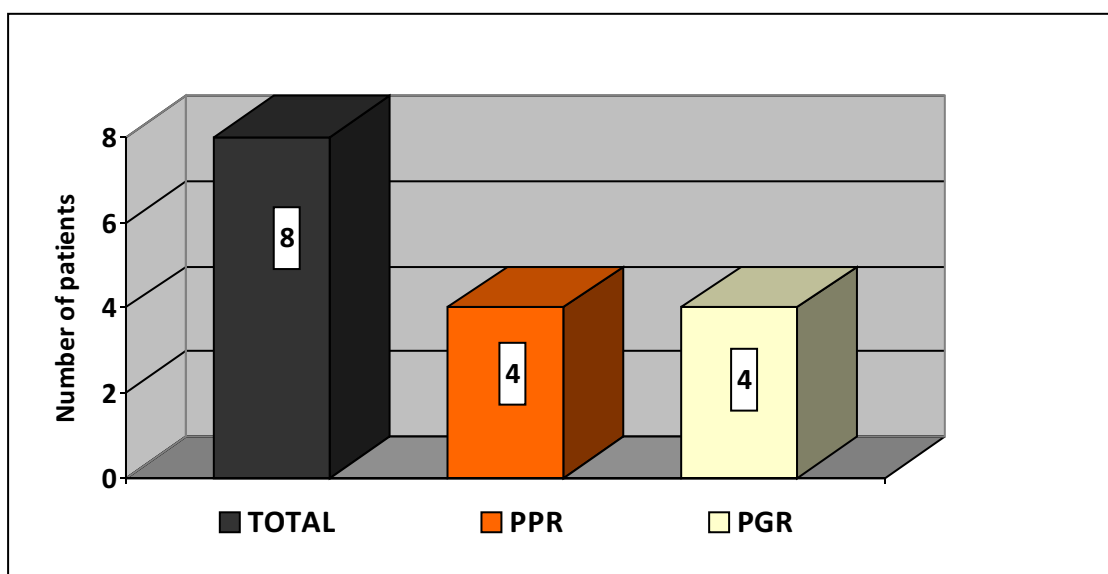


Fig. 3 Prednisone response type

Treatment was performed according to protocol ALL BFM 95. Patients with Ph cr disease were included in the high-risk group and patients who did not get initial molecular cytogenetic investigation in the medium-risk group. 50% (4 / 8) of patients had a favorable response to treatment with prednisone (PGR) (Figure 3). A good response to induction therapy had only 37.5% (3 / 8), the remainder being classified as late-responders (3 / 8) / non-responders (1 / 8). In one case death occurred before day 33 due to a severe systemic infection.

One patient was monitored for minimal residual disease (MRD) and its persistence in the context of complete hematological remission required treatment with tyrosine kinase inhibitor. The MRD level became undetectable after 2 years and 10 months of Gleevec treatment. 1 year after Gleevec suppression, therapy reintroduction, was required due to detectable levels of MRD. Currently the patient is in complete remission under Gleevec treatment.

One of the patients that was not tested at initial diagnosis presented late bone marrow and CNS relapse. The Ph CR was detected and in absence of a matched family donor, the Proposal Orlando protocol was initiated (imatinib courses alternating with HR type chemotherapy blocks, followed by maintenance treatment with Gleevec, methotrexate and 6-mercaptopurine). At 10 months after the suppression of Gleevec therapy, a second relapse, (this time a Ph cr negative) was diagnosed. The treatment was performed according to the protocol for relapsed ALL, but after 8 months a treatment resistant relapse occurred, resulting in patient death.

In the third case the patient was considered as an induction therapy non-responder and, due to the fact that a matched family donor was available, he benefit from an allogeneic HSCT. 2 years after HSCT he presented relapse. After achieving complete remission, Gleevec therapy was initiated. Since the patient presented at 9 months on imatinib mesylate therapy a second relapse, the regimen was switched on second generation tyrosine inhibitor (Dasatinib) and the patient is currently in hematologic remission. A second allogeneic HSCT is prepared, from an matched unrelated donor this time.

Another patient benefit from HSCT from a matched unrelated donor. Complete remission was achieved, but he died 6 months after transplantation due to a severe herpes simplex virus systemic infection.

Due to the low number of patients presenting this cytogenetic abnormality we could not perform correlations between various parameters and evolution. However, we noticed that in our study group all patients with PPR were ultimately non-responders or late-responders.

Of the 8 patients currently only 2 are alive, and both benefit from imatinib mesylate, imatinib mesylate and dasatinib respectively treatment. In one case death occurred due to resistant disease; in the remaining cases it is caused by severe infection (pulmonary invasive aspergillosis, sepsis with *Pseudomonas aeruginosa*, severe herpes simplex virus (HSV) systemic infection, febrile neutropenia of unspecified etiology) (Figure 4).

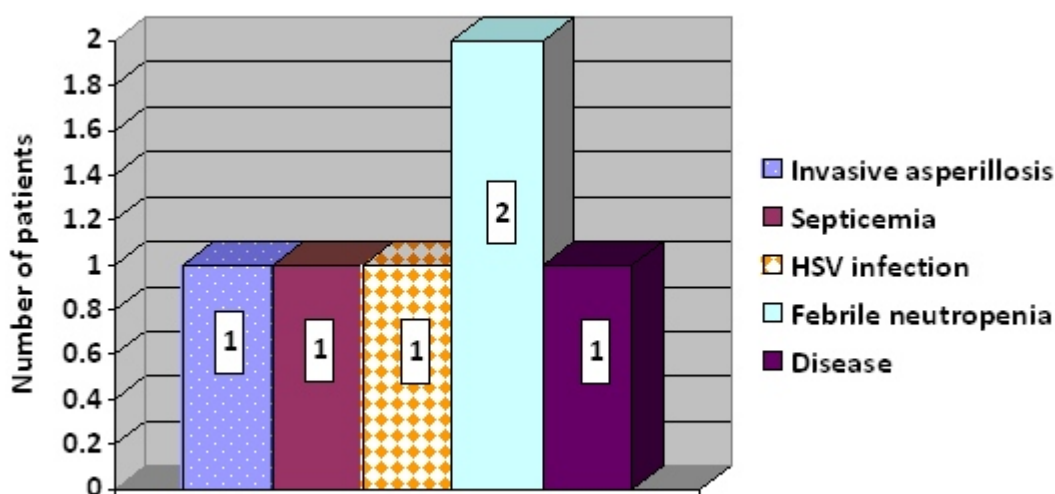


Fig. 4 Causes of death

DISCUSSIONS

Therapeutic plan include in patients with Ph cr positive ALL a search for suitable hematopoietic stem cell donor for an allogeneic HSCT. If no matched donor was found, tyrosine kinase inhibitors is a therapeutic option that allowed a significant increase in life expectancy.

The two patients who were detected positive for Ph cr at disease relapse were probably incorrect classified as medium-risk group (MR), and undertreated. Consequently, long-term results are unsatisfactory and prognosis is poor.

Infection represented the cause of death in majority of cases. This observation reveals the fact the supportive therapy of these patients that are treated following aggressive chemotherapy protocols should be improved, in order to allow us to perform the leukemia treatment at efficient doses in optimal timing.

CONCLUSIONS

1. Although overall survival in childhood ALL currently stands at over 80%, our experience shows that Ph cr positive ALL remain, despite new therapeutic modalities, a malignant disease with extremely reserved prognosis. Still, allogeneic HSCT and alternative therapy protocols may offer a chance for increased survival in these patients.
2. HSCT and treatment with tyrosine kinase inhibitors may be alternatives for the induction of continuous complete remission, but does not provide cure certainty.
3. A very important place in the long-term follow-up of these patients with molecular abnormalities is occupied by MRD assessment. It allows early therapeutic intervention before the clinical and/or hematological relapse, thereby increasing chances of survival for these patients.

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