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Imatinib Treatment Alone in Philadelphia-Positive Acute Lymphoblastic Leukemia: Is It Enough?

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Abstract

BCR-ABL fusion gene t(9;22)(q34;q11) occurs in only 3% of pediatric acute lymphoblastic leukemia (ALL) cases. Previously, less than 40% of Philadelphia-positive ALL patients were cured with intensive chemotherapy. The use of imatinib (340 mg/m²/day) added to an intensive chemotherapy regimen has improved the outcome in this population at 3 years to an event-free survival of 80%. Imatinib treatment alone was administered after remission induction chemotherapy to a patient with Philadelphia-positive ALL who presented with serious chemotherapy toxicity, so that intensive chemotherapy could not be maintained. This is the only patient in the literature who survived remission for more than 2.5 years with imatinib treatment only.

Introduction

BCR-ABL fusion gene t(9;22)(q34;q11) occurs in only 3% of pediatric acute lymphoblastic leukemia (ALL) cases. This is in contrast to adult ALL where this translocation is present in 25% of cases and 95% of adult chronic myelogenous leukemia (CML) cases. In pediatric BCR-ABL-positive ALL, the BCR breakpoint produces a 190-kb protein (p190) in contrast to CML, where a different protein (p210) is usually produced. The t(9;22) in pediatric ALL is usually associated with older age, higher white blood cell (WBC) count, and frequently central nervous system involvement at diagnosis. Previously, less than 40% of Philadelphia-positive ALL patients were cured with intensive chemotherapy. The use of imatinib (340 mg/m²/day) added to an intensive chemotherapy

regimen has improved the outcome in this population at 3 years to an event-free survival of 80% [1].

Case Report and Methods

A 14-year-old girl who presented with fatigue, nose bleeding, generalized ecchymosis over the body and arthralgia was admitted to our hospital. On physical examination she had pallor, tachycardia, dermal/mucosal petechiae and ecchymosis. The liver was 6 cm and the spleen was 4 cm palpable below the mid-costal line. Hematological examination revealed a total leukocyte count (WBC) of $333,000/\text{mm}^3$, a hemoglobin level of 4 g/dl, and a platelet count of $29,000/\text{mm}^3$. Peripheral blood smear (PBS) revealed 97% L1-type blasts. In immunohistochemical staining the blastic cells were myeloperoxidase negative. Pre-B-cell ALL was detected by immunophenotyping. Transaminases, blood urine nitrogen, creatinine, uric acid and phosphor were within the normal range, only lactate dehydrogenase was high (2,970 IU/ml). Leukopheresis was performed two times because of hyperleukocytosis. Lumbar puncture was done when leukocyte count decreased to $50,000/\text{mm}^3$ (on the 4th day). No cells were seen in the cerebrospinal fluid and benign cytology was reported by pathology.

A modified BFM protocol, Turk ALL 2000, was given to the patient. The PBS smear on the 8th day revealed poor steroid response (blast count at PBS was $1,395/\text{mm}^3$). No hematologic remission occurred in bone marrow aspiration at the 15th day (blast rate was 27%) and at the 33rd day (blast rate was 12%). The patient was included in the high-risk group of the treatment protocol. BCR-ABL fusion gene was found to be positive and the cytogenetic analysis of the first-day bone marrow aspiration revealed t(9;22) in 11 out of 20 metaphases.

The first course of High Risk (HR1) block therapy was given following induction therapy. After completion of the first HR1 block, imatinib (Glivec® 400 mg/m²/day per os) was started. Severe mucositis developed and she was put on total parenteral nutrition (TPN). She had a severe intractable gastrointestinal hemorrhage and required several units of erythrocyte and platelet transfusion. During this period she developed very severe neutropenia. Her fever reached 39°C, and C-reactive protein (CRP) was found to be positive (26 mg/dl, N: <0.5 mg/dl). The first HR2 block treatment could not be started, but imatinib treatment was given regularly. In the bone marrow aspiration which was done 37 days after the first HR1 block had been completed, remission was seen. The patient showed a depressive mood and no verbal cooperation. In the neurologic examination, decreased muscle strength, increased muscle tone and deep tendon reflex were found in all extremities and Babinski test was positive. Cranial magnetic resonance imaging was normal. After 43 days of the first HR1 block, severe mucositis, hemorrhagic diarrhea, typhilitis and hyperemesis were still ongoing and she was on TPN. At follow-up, after a severe, abundant gastrointestinal hemorrhage, she suddenly developed unconsciousness. At physical examination, her Glasgow coma score was 7, cardiac pulse was 34/min, arterial blood pressure was 70/30 mm Hg, capillary perfusion time was 3 s and she was hypothermic. Laboratory results of the patient were found to be as follows: WBC $2,030/\text{mm}^3$, absolute neutrophil count $1,640/\text{mm}^3$, hemoglobin 5.09 g/dl, platelets $44,000/\text{mm}^3$, CRP 6.8 mg/dl, urea 113 mg/dl, creatinine 0.9 mg/dl, glucose 136 mg/dl, AST 77 IU/l, ALT 91 IU/l, bilirubin 0.3 mg/dl, GGT 88 IU/l, prothrombin time 17.6 s, INR 1.4, activated partial thromboplastin time 43 s, D-dimer 1,211 ng/ml, fibrinogen 190 mg/dl, and blood electrolytes were normal. Blood gas analysis revealed metabolic acidosis (lactic acid: 12.6 mmol/l). She was transferred to the Pediatric Intensive Care Unit. Intensive fluid replacement, positive inotropic support, erythrocyte and thrombocyte suspensions were given. Left ventricular ejection fraction was found to be 64% by echocardiography. Because of the possibility of sepsis and septic shock broad spectrum antibiotherapy was started. The encephalopathy progressed and generalized tonic-clonic convulsions occurred. Then she was intubated and mechanically ventilated. Cranial computed tomography showed a 9-mm bleeding region and peripheral edema in the left basal ganglion. Despite all this supportive treatment and intensive replacement with NaHCO₃ for 12 h, lactic acidosis progressed and lactic acid levels reached up to 20 mmol/l. Hemodiafiltration (HDF) was performed. In the etiology of lactic acidosis, thiamine deficiency secondary to long-term TPN without vitamin B complex was considered and 4 × 25 mg/day intravenous thiamine treatment was started. With the help of HDF (one episode) and thiamine therapy lactic acidosis regressed rapidly and normalized. Thiamine treatment was given regularly for 3 months, and lactic acidosis never developed in the follow-up.

Results

Because of transfusion-dependent anemia and thrombocytopenia, prolonged febrile neutropenia, persistent severe mucositis and related gastrointestinal hemorrhage, encephalopathy and convulsions, chemotherapy could not be continued. Two months after the first HR1 block chemotherapy had been completed, bone marrow examination was re-evaluated. The bone marrow was in remission and the BCR-ABL gene fusion was negative. The patient was followed up under mechanic ventilation for 1 month and then extubated. Percutaneous endoscopic gastrostomy (PEG) was performed because she could not feed orally for 4 months and she developed swallowing dysfunction. After staying for 54 days in the intensive care unit, the patient was taken to the hematology service.

Her cognitive functions returned back to normal after 6 months. Mucositis showed slow regression over months. Physiotherapy was regularly performed for spastic tetraparesis. Nine months after the diagnosis, the patient was sent home while she was still on imatinib therapy. She never had convulsions again. Nine months after discharge, she started walking with support. Twelve months after discharge, she was able to walk by herself without any support. Five months after the PEG was opened, she started to feed orally and the PEG was closed.

Imatinib 400 mg/m²/day was administered regularly. Six months after the first HR1 block chemotherapy, she did not need any transfusion. Bone marrow examination was performed every third month, and morphological and molecular remission was observed at each evaluation. Neither in her family nor outside her family a matched donor could be found. Thirty months after the diagnosis, she is still in morphological and molecular remission.

Discussion

Previously, less than 40% of Philadelphia-positive ALL patients were cured with intensive chemotherapy. Several studies have reported early results of the addition of imatinib to combination chemotherapy [2–5]. A consistent feature of all these studies is the increased complete remission rate. Where relevant to the study population, the higher complete remission rate typically translates into an increased allogeneic transplant rate. In a study reported by GIMEMA [6], a combination of imatinib and steroids resulted in all patients (median age 69 years) achieving hematologic complete remission, with a median survival from diagnosis of 20 months. Although it is now clear that imatinib can be safely and effectively combined with other chemotherapeutic drugs, it is far from clear whether and how it should be combined with allogeneic HSCT. The current working assumption is that best outcomes in Philadelphia-positive ALL are achieved when tyrosine kinase inhibitors are used as a bridge to transplant. However, a recent provocative study of imatinib in childhood ALL has challenged this assumption.

Chemotherapy could not be resumed after the first HR1 block chemotherapy in our case because of transfusion, which was necessary due to anemia and thrombocytopenia, prolonged febrile neutropenia, stage-4 mucositis and related gastrointestinal hemorrhage, encephalopathy and convulsions. Because of serious chemotherapy toxicity, only imatinib (400 mg/m²/day) treatment was given to our patient with Philadelphia-positive ALL after remission induction chemotherapy.

In conclusion, this is the only pediatric patient in the literature who survived remission with only imatinib for more than 2.5 years. Imatinib treatment only, as in CML patients, instead of combined chemotherapy is encouraging for pediatric Philadelphia-positive ALL patients. However, further studies are required to suggest imatinib treatment alone in pediatric Philadelphia-positive ALL.

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