Imatinib Mesylate (Glivec) in Pediatric Chronic Myelogenous Leukemia

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Abstract

Introduction: Imatinib Mesylate is a selective inhibitor of TK and is considered now to be the frontline therapeutic agent during the chronic phase of CML. We have evaluated the efficacy of it on children with chronic-phase of CML.

Patients and Methods: In a clinical trial study over the past 3 years, 14 patients (8 females and 6 males, 2.5-14 years old) were admitted with a diagnosis of CML. Seven patients who were in the early chronic-phase and seven who were in the late chronic-phase suffered from hematological relapse while being treated with conventional therapy. All of them had positive BCR-ABL in peripheral blood and bone marrow. Glivec was given as an oral dose of 300mg/m^2/d. Then, regular monitoring was done for hematological and cytogenetic response, toxic effects, disease progression and survival.

Results: All seven patients with newly- diagnosed CML and five previously treated patients attained complete and sustained hematological and cytogenetic remission in a follow-up period over 2 to 30 months (the mean was 22.5). One patient was taken off study because of drug intolerance. One patient in each group relapsed after initial response and died from progressive disease. Overall survival was 86%. No major side effects were noted and there was no drug- related mortality.

Conclusion: Glivec has proved to be effective in inducing prolonged complete hematological and cytogenetic remission in newly- diagnosed as well as previously treated children with CML. One major problem is prolonged, unlimited and continued therapy which results in poor compliance as time goes by. In addition, in developing countries, high cost and suboptimal accessibility would make its routine use quite difficult.

Keywords: Imatinib Mesylate, CML, Tyrosine Kinase

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Introduction

Chronic myelogenous leukemia (CML) is primarily a disease of middle age; the peak incidence is in the fourth and fifth decades. Most pediatric CML cases are diagnosed after 4 years.(1) In pediatric groups, significant racial or sexual predilection does not historically exist;(1) the disease is characteristically divided into three phases: chronic, accelerated, and blast phase.(1, 2) The cause of CML is the translocation of regions of the BCR and ABL genes to a BCR-ABL fusion gene. Indeed, it is a reciprocal translocation of the cytogenetic hallmark of CML (i.e.; ph chromosome) termed t (9; 22).(1, 3) The product of this gene, which is the BCR/ABL protein, is an active protein tyrosine kinase. This protein plays a significant role in cell growth regulation.(4, 5)

Allogeneic full-match sibling donor BMT is the only well- documented curative therapy for children and adult patients with CML.(6, 7, 8) Because of the low numbers of suitable donors (fewer than 30 percent), this method actually does not prove to be efficient.(8) Also, conventional chemotherapy is only effective in 5 to 20 percent of cases (i.e.; complete cytogenetic response) and it is associated with serious toxic effects.(9, 10)

Imatinib mesylate (Glivec, Novartis, Basel, Switzerland) was formerly called ST1571.(11)

This drug is a potent, selective, competitive inhibitor of the BCR-ABL, protein tyrosine kinase.(2) In this study, we decided to evaluate the efficacy and safety profile of Imatinib on a group of newly- diagnosed patients in the treatment- failure phase of CML.

Materials and Methods

Study patients: Patients were suitable for this study if they were younger than 16 years of age and had chronic-phase, ph-chromosome-positive CML that had been newly- diagnosed (within the early chronic-phase) or had failed to respond to previous treatment (i.e., they were in the late chronic-phase), according to one of the criteria described below. The chronic phase was defined by all of the following criteria: 1) the presence of less than 15 percent blasts, 2) the presence of less than 20 percent basophiles, 3) the presence of less than 30 percent blasts plus promyelocytes in the peripheral blood and marrow and 4) a platelet count of at least 150,000/mm^3. Hematologic failure was defined as having one of the following criteria: 1) hematologic resistance (failure to achieve a complete hematologic response, with white-cell counts increased to at least 20/000/mm^3 during therapy. Cytogenetic failure were defined as one of the following criteria: 1) cytogenetic resistance (persistent positive BCR/ABL during at least one year of therapy), or 2) relapse after a major cytogenetic response had been achieved. If BCR/ABL became positive again, a relapse was considered to have occurred. The presence of any nonhematologic toxic effects of grade 3 or higher was defined as an intolerance of Imatinib (as defined by the National Cancer Institute Common Toxicity Criteria, in which a grade of 0 indicates no adverse events and a grade of 5, life- threatening events) that persisted for more than one month during therapy with an optimum dose of the drug.

Patients were assayed for levels of liver aminotransferases, serum bilirubin, and serum creatinine that were no higher than twice the upper normal limit. Patients were excluded from the study if their Eastern Cooperative Oncology Group performance score was 3 or higher (poor), or if they were in the New York Heart Association functional class III or IV. Also, patients were excluded if they had received treatment with hydroxyurea within seven days, interferon or cytarabine with 14 days or any other investigational agent within 28 days before starting the study treatment.

All patients had been given written informed consent according to institutional regulations. The study was performed in accordance with the Declaration of Helsinki.

Study design and treatment: In this single-group unicenter, clinical trial study, patients received imatinib in a oral dose of 300 mg/m^2/day. If complete hematologic response had not been achieved after 3 months of treatment, the imatinib dosage was increased to 300mg/m^2 twice daily. Also, if the disease relapsed within 3 months after the achievement of as complete hematologic response or a major cytogenetic response had not been achieved after 12 months of therapy, the imatinib dosage was increse.

The study was designed by the investigators and representatives of the sponsor, Novartis and Mahak Charity Institution. The data were collected and statistically analyzed by SPSS-Ver 11. Cytogenetic studies were performed at the cytogenetic laboratory centers of Dr. Kariminejad and Dr. Farhadi.

Dose modifications because of side effects: Dose modifications of the drug were done if the following events occurred:

1. Discontinuation of therapy after occurrence of and continuation of grade 2, nonhematologic toxic effects during treatment, until amelioration to grade 1 or better and restarting at the original dose.
2. Interruption of treatment after the recurrence of grade 2 toxic effects until amelioration to grade 1 or better. Then, treatment was begun at the reduced daily oral dose of 200mg/m^2.
3. Discontinuation of treatment if the patient developed grade 3 or 4 nonhematologic toxic effects until amelioration to grade 1 or better. Then, treatment was begun at the reduced daily dose of 200mg/m^2.
4. Interruption of treatment after developing a grade 3 or 4 hematologic, toxic effect (a neutrophil count of less than 1000/mm^3, or a platelet count of less than 50000/mm^2) until amelioration of the effect to grade 2 or better. Than the same dose was begun if the effect had reached a grade 2 level within two weeks. But, a reduced daily dose of 200mg/m2 was prescribed if a grade 3 or 4 of the toxic effect had persisted for more than two weeks.

Blood transfusions, at the discretion of the investigator, were prescribed in patients with anemia.

Evaluation of patients: For an exact evaluation of all enrolled patients, a complete blood count and a differential analysis it was obtained weekly for the first 12 weeks. Then, this measurement was done every other week for the next 12 weeks, and every 6 weeks thereafter. Also, bone marrow morphology and cytogenetic were evaluated every 24 weeks, when extramedullary involvement was also evaluated by a physical examination. Adverse events were evaluated at each visit and graded

Table-1. Patients characteristics.

Variables	Patients with Chronic-Phase CML		All Enrolled Patients
	Early Phase	Late Phase	
Age (yr)			
Median	11	5.5	9.5
Range	8-14	2.5-10	2.5-14
Sex			
Male	3	3	6
Female	4	4	8
Splenomegaly	6	4	10
Hepatomegaly	2	1	3
Lymphadenopathy	1	1	2
Extramedullary Disease	1	-	1
WBC count			
Median	209200	85200	206100
Range	48700-775000	50900-429000	48700-775000
Platelet count			
Median	348000	461000	460000
Range	112000-1455000	256000-937000	112000-1455000
Hemoglobin			
Median	10.2	10.4	10.2
Range	8.3-13.5	7.5-12.6	7.5-13.5
Time since diagnosis(mo)			
Mean	0.3	53	26.6
Median	0.2	48	15.35
Range	0.1-0.7	30-84	0.1-84
Previous therapy(mo)			
Mean	0.3	53	26.6
Median	0.2	48	15.35
Range	0.1-0.7	30-84	0.1-84
Follow up(mo)			
Mean	13.42	19.71	16.57
Median	10	24	16.5
Range	6-24	2-30	2-30

Table- 2. Cytogenetic and Hematologic Responses In Patients with Chronic-Phase CML

Response	All Patients (in numbers)	Early phase[2] (in numbers)	Late phase[3] (in numbers)
Complete Cytogenetic Response (negative BCR/ABL)	12	6	6
Complete hematologic response	13	7	6
No Response	2	1	1

[1]The level of cytogenetic response was defined by BCR/ABL positivity in bone marrow sample.
[2]Starting treatment before 6 months since diagnosis.
[3]Starting treatment after 6 months since diagnosis.

according to the National Cancer Institute Common Toxicity Criteria.

The rate of major cytogenetic response was used for the primary efficacy end point, which was categorized as either complete (negative BCR/ABL) or partial (weekly positive BCR/ABL). Another category of cytogenetic response was no response (i.e. positive bcr/abl). For an evaluation of a cytogenetic response, a BCR-ABL fusion product was determined by the RT-PCR method in peripheral blood and bone marrow of all enrolled patients.

The end points of secondary efficacy included the rate of complete hematologic response, the time to progression, and overall survival. Complete hematologic response was defined by all of the following criteria:

1. White-blood cell count of less than 1000/mm^3
2. Platelet count of less than 450000/mm^3
3. The presence of less than 5 percent myelocytes and metamyelocytes and less than 20 percent basophiles in peripheral blood
4. The absence of blasts and promyelocytes in peripheral blood
5. The absence of extramedullary involvement.

Accelerated-phase CML was defined by one of the following criteria:

1) The presence of 15 to 29 percent blasts in blood or marrow,

Table- 3. Common adverse events

Events	Number of Patients with adverse event	
	Any Grade	Grade 3 or 4
Complications	13	1
Non-Hematologic		
Superficial Edema	6	-
Nausea	7	1
Vomiting	7	1
Muscle cramps	3	-
Weigh gain	8	-
Myalgia	4	-
Arthralgia	4	-
Abdominal pain	3	-
Musculoskeletal pain	8	-
Dyspnea	2	-
Hematologic	4	2

2) The presence of at least 30 percent blasts plus promyelocytes in blood or bone marrow, or

3) The presence of least 20 percent basophiles in blood.

Blast-phase CML was defined by the presence of at least 30 percent blasts in blood or marrow or the presence of extramedullary blastic disease. Time to progression, was defined as one of the following criteria: 1) the time for the start of treatment to the onset of an accelerated or blastic phase, 2) discontinuation of therapy because of unsatisfactory therapeutic effect, or 3) death. Survival was calculated from the beginning of therapy until the time of death from any cause.

Statistical analysis: We aimed to demonstrate a major cytogenetic response rate of at least 20 percent among patients with newly diagnosed CML and at least 30 percent among those with previous treatment failure. Time to progression and survival were computed with the use of standard Kaplan-Meier methods. Because of small number of patients studied, we decided to use non-parametric tests for statistical analysis.

Results

Patients and Treatment: A total of 14 patients were selected for analytical treatment at Ali-Asghar Children's Hospital Medical Center between September, 2001 and December, 2004; data were collected through October, 2004 (Table -1). The diagnosis of chronic-phase CML was confirmed in all fourteen of these patients (100 percent) after a complete review of data. The characteristics of the patients were typical of patients with previous treatment failure, late-chronic-phase CML,(7 patients), or newly- diagnosed patients, early-chronic phase CML (7 patients), (see Table- 1). The median duration of treatment with Imatinib was 22.5 months (the range was 2 to 30 months); this duration for early and late chronic-phase CML was 12 months (the range was 6 to 24 months) and 30 months (the range was 2 to 30 months); months; about 90 percent of the patients were treated for at least 12 months. Of the 14 patients whose treatment was analyzed, 86 percent are still receiving Imatinib treatment and two patients discontinued therapy because of the progression of the disease (one patient), and adverse event (one patient).

Efficacy: Of the 14 patients with a confirmed diagnosis of chronic-phase CML, 13 (nearly 93 percent) had a major cytogenetic response (negative BCR/ABL) and 1 (7 percent) did not respond. Cytogenetic response rates were higher among patients who had newly- diagnosed (early chronic-phase) CML than patients with hematologic resistance (late chronic-phase) CML.

Of the 13 patients in whom a major cytogenetic response was achieved, 12 (92 percent) continue to have such a response as of the last follow-up, whereas the other (8 percent) had a cytogenetic relapse (defined as positive BCR/ABL). This patient had a relapse five months after the beginning of Glivec therapy due to persistent uncontrolled vomiting and the discontinuation of treatment.

Complete hematologic responses were reported in 13 of the 14 patients studied (92 percent) (Table 2). The median time before a complete hematologic response in both groups of early and late chronic-phase CML patients was 2 months (the range was 21-118 days); 83 percent (10 patients) of the patients who had a response did so within 72 days. The estimated rate of progression-free survival at 30 months was 85.71 percent (95 percent confidence interval, 76.3 to 95 percent) [Fig.1]. This rate for early chronic-phase CML patients (100%) was better than for late chronic-phase

patients (71.43 17.07% with 95 percent confidence interval).

Prognostic Factors: Because of the few numbers of CML childhood cases in this study, an analysis of the association between base-line variables (which had been noted for adult patients)(1) and the rate of major cytogenetic response was statistically impossible.

Safety: Common adverse events included superficial edema, nausea, vomiting, weight gain, and musculoskeletal pain (Table- 3). Grade 3 or 4 adverse events were infrequent; the most common grade 3 or 4 event was nausea and vomiting, and pancytopenia (Table 3). Grade 3 or 4 neutropenia and thrombocytopenia was noted during the study in two patients while they were using high-dose therapy. Their condition improved after discontinuation of therapy for two weeks (Table 3).

Severe drug-related adverse events led to the complete discontinuation of therapy in one patient (7.14 percent). Other serious, drug-related, adverse events were not reported in all the subject patients, febrile neutropenia and fluid retention was seen in only one patient. These two events were developed when high-dose therapy was used. Other drug-related adverse side effects which occurred with less frequency were muscle cramps, myalgia, artheralgia, abdominal pain, and dyspenea. Two patients with progressive disease in blastic phase, died after the discontinuation of therapy. No patients died from drug toxicity.

Discussion

In this phase 2 study of the use of Imatinib mesylate in patients with chronic-phase CML (in whom previous treatment had failed), the rates of major cytogenetic response (negative BCR/ABL) were about 79 percent. This was significantly better than the response to the previous treatments (p=0.02). Treatment was well tolerated; serious drug-related non-hematologic adverse events occurred in less than 8 percent of the patients, and hematologic toxic effects were manageable.(13, 14)

The rate of major cytogenetic responses we observed were higher than those reported in patients treated with conventional therapy.(2, 9, 15, 16) The estimated rate of 30-month progression-free survival rate of 86 percent is also higher than in trials of conventional therapy. Our results cannot be attributed to a bias since all confounding variables were at least in this study.(1, 2, 9, 11, 15)

Because Imatinib is well tolerated, it may be feasible to combine it with other agents to treat interferon-resistant CML in the late chronic phase or to optimize the status of the disease before performing allogeneic stem-cell transplantation.(16, 17) In this study, two females from early chronic-phase group had full-matched sibling donor. They had allogeneic stem-cell transplantation while in complete hematologic response in one patient and complete hematologic and cytogenetic response in another patient with Glivec. In this study, disease progression occurred in nearly 7 percent of patients (one patient from late chronic-phase group) within 30 months. In spite of doing intensive combined chemotherapy for blastic phase of CML, she died after 2 months Glivec therapy.

Regimens that combine Imatinib with other agents may further improve results, and ongoing clinical trials are testing the feasibility of these approaches.(16, 18)

The efficacy of Imatinib is also being investigated in patients with newly- diagnosed CML. All seven participating patients with early chronic-phase CML achieved complete hematologic response (100%) with Glivec therapy. One patient with an initial white blood cell count of 700000 per mm^3 who was in this group was treated only with Imatinib. She was in complete hematologic response after three months of beginning therapy. Another six patients of this group achieved complete cytogenetic response (nearly 86 percent).(18)

Note added in proof: Follow-up data was available for 12 patients as of November 30, 2004; that is, 36 months after starting the study (the median follow-up period was 28.5 months). Among these patients, one patient from an early chronic-phase, suffered from vomiting. She had progressed to blastic phase of CML and died despite intensive combined chemotherapy.

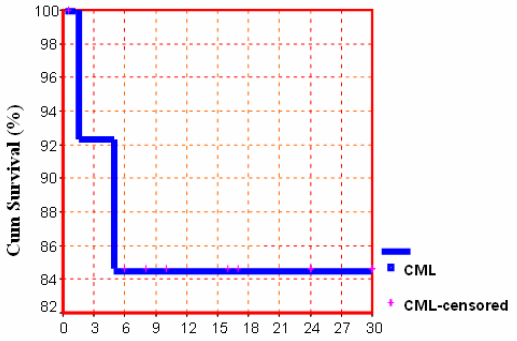

Figure-1. Event-Free survival of children with chronic phase CML. Follow up duration (mo)

Conclusion

Imatinib Mesylate has proved to be effective in assisting in complete hematologic and cytogenetic remission in newly- diagnosed as well as previously treated children with chronic-phase CML. It is well tolerated and has not caused any major toxic side effects in treated children. One major problem is prolonged, unlimited and continued therapy which results in poor compliances as time goes by. Also, in developing countries, the high cost and suboptimal accessibility makes its routine use quite difficult.

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