National PBM Drug Monograph

Imatinib Mesylate (Gleevec™)

Addendum April 2003

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

http://www.vapbm.org/monograph/imatinibcmonograph.pdf

Introduction

Imatinib is a potent inhibitor of tyrosine kinases associated with the abnormal BCR-ABL gene fusion product. The BCR-ABL gene is the result of a translocation of t(9,22), also known as the Philadelphia chromosome (Ph), and is found in more than 90% of patients diagnosed with chronic myelogenous leukemia (CML). Previously, imatinib has demonstrated the ability to induce complete hematologic responses and major cytogenetic responses in patients who had failed to respond to interferon and cytarabine during the chronic phase of CML. Recently, a phase 3 trial comparing imatinib to interferon and cytarabine in newly diagnosed, untreated patients with CML in chronic phase was completed.

Study goals

The primary endpoint was progression, defined as: death from any cause during treatment, development of accelerated-phase CML or blast phase, loss of hematologic response, loss of major cytogenetic response, or an increasing white blood cell count.

Secondary endpoints: rate of complete hematologic response, rate of major cytogenetic response, safety, and tolerability.

Methods

In a prospective, phase 3, multi-centered, randomized trial patients received either interferon and cytarabine or imatinib.

Interferon: Gradually escalating SQ doses to the target of 5 million units/m^2 per day (if toxicities were <grade 3).
Cytarabine: SQ doses of 20mg/m^2 (maximum dose of 40mg) for 10 days each month when maximally tolerated dose of interferon was achieved.

Imatinib: 400mg orally every day.

N.B. Hydroxyurea was allowed for both arms during the first six months to help keep white blood cell counts <20,000/mm^3

Dose Modifications

Imatinib: If no complete hematologic response by 3 months or at least a minor cytogenetic response at 12 months, increase dose to 400mg bid.

Cytarabine: If receiving the maximally tolerated interferon dose, and no complete hematologic response at 3 months or at least a minor cytogenetic response at 12 months, increase up to 40mg/day for 15 days each month.

Crossover

Patients were allowed to crossover if: there was no response, a loss of response, an increase in the white blood cell count, or could not tolerate therapy (recurrence of nonhematologic toxicity of at least a grade 3 despite dose reductions and symptom management).

Data Analysis

The primary endpoint was analyzed by an intention-to-treat analysis; all other parameters were analyzed only until patients crossed over or discontinued therapy.

Criteria

Inclusion:

- 18-70 years old
- chronic-phase, PH-positive CML
- previously untreated except for hydroxyurea or anagrelide
- liver aminotransferases, serum bilirubin, serum creatinine no higher than 1.5 times ULN

Exclusion:

- extramedullary disease other than hepatosplenomegaly
- <100,000 platelets unrelated to therapy
- women who were breast feeding, pregnant, or of childbearing potential without a negative pregnancy test
- ECOG performance status of 3 or more
- Other uncontrolled serious medical conditions
- Prior chemotherapy or any investigational drug
- Prior hematopoietic stem cell transplant
- Surgery within the past 4 weeks
- HIV positive
- History of another cancer within 5 years

Results

Table 1. Baseline Criteria

Characteristic	Imatinib (n = 553)	Interferon plus cytarabine (n = 553)
Age- median	50	51
Sex (%)		
Male	61.7	56.1
Female	38.3	43.9
ECOG performance status (%)		
0	76.9	74
1	20.8	21.9
2	1.4	2.0
missing	0.9	2.2
Interval since diagnosis (mo)		
Median	2.1	1.8
Chromosomal abnormalities in addition to Ph (%)		
No	82.5	88.2
Yes	12.1	7.6
Splenomegaly (%)	23.0	27.1
WBC $x10^{-3}/mm^3$		
Median	17.9	20.2
Platelet count $x10^{-3}/mm^3$		
Median	336	340

Table 2. Treatment Status[†]

Variable	Imatinib	Interferon plus cytarabine
Continued initial treatment (%)	85.7	10.8
Discontinued initial treatment	12.3	31.6
Disease Progression (no. of pts)	18	29
Adverse events	12	33
Proceed to allogeneic transplant	8	7
Withdrew consent	12	75
Crossed over to alternative arm (%)	2	57.5
Disease Progression (No. of pts)	6	63
Intolerance of treatment	4	136
No CHR at 6 mo	0	41

No CHR or MCR at 12 ms	1	53
Continued alternative treatment (No.)	6	284
Discontinued alternative treatment	5	34

† Median follow-up of 19 months

Table 3. Observed Hematologic and Cytogenetic Responses

Response	Initial Treatment		Crossover Treatment	
	Imatinib (n=553)	IFN + cytarabine (n=553)	From Imatinib to IFN + cytarabine (n=11)	From IFN + cytarabine To imatinib (n=318)
Complete hematologic	95.3 (93.2-96.9)	55.5 (51.3-59.7)†	27.3 (6.0-61.0)	82.4 (77.7-86.4)
Major cytogenetic	85.2 (81.9-88.0)	22.1 (18.7-25.8)†	0 (0-28.5)	55.7 (50.0-61.2)
Complete	73.8 (69.9-77.4)	8.5 (6.3-11.1)†	0 (0-28.5)	39.6 (34.2-45.2)
Partial	11.4 (8.9-14.3)	13.6 (10.8-16.7)	0 (0-28.5)	16.0 (12.2-20.5)

†p<0.001 for comparison to imatinib group

Table 4. Disease Progression and Survival

Outcome	Imatinib	Interferon + cytarabine
Progression-Free Survival		
12 months	96.6	79.9†
18 months	92.1	73.5†
Survival Rate		
18 months	97.2	95.1

† p<0.001

Adverse Events

Adverse events were consistent with previous clinical trials. Patients in the imatinib group had primarily grade 1 or 2 events with rare grade 3 or 4 toxicities. Patients in the interferon + cytarabine group had more grade 3 or 4 toxicities consistent with the high number of crossovers to the imatinib arm.

Conclusion/Recommendation

The management of newly diagnosed patients with Chronic Myelogenous Leukemia has changed. Until this time, the gold standard for treatment has been the combination regimen of cytarabine and interferon. Recent data from a Phase III trial comparing imatinib vs. cytarabine and interferon has shown superior outcomes with imatinib therapy. These outcomes include cytogenetic response, hematologic response, tolerability and freedom from progression to advanced phases of CML. Based on this data, imatinib should be considered first-line therapy for CML.

Allogeneic stem cell transplantation, a procedure with significant morbidity and mortality, is still considered the only curative treatment. For this reason, patients who may be potential candidates for transplant should be offered this option due to the potential for imatinib-failure or loss of response. The durability of response with imatinib is unknown at this time, but maturity of this data and others will provide insight on this issue.

Reference

O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. for the IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. NEJM 2003;348:994-1004.

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