Published in final edited form as:

Leuk Res. 2009 June ; 33(6): 837–839. doi:10.1016/j.leukres.2008.10.004.

IMATINIB HAS LIMITED THERAPEUTIC ACTIVITY FOR HYPEREOSINOPHILIC SYNDROME PATIENTS WITH UNKNOWN OR NEGATIVE PDGFR α MUTATION STATUS

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Abstract

Hypereosinophilic syndrome (HES) is characterized by sustained non-clonal blood and tissue eosinophilia, leading to end-organ damage. With a molecular/cytogenetic clonality marker, the disease is classified as chronic eosinophilic leukemia (CEL). Efficacy of imatinib mesylate is well established in CEL with FIP1L1-platelet derived growth factor- α (PDGFR α) rearrangement. We treated with imatinib 18 HES patients (11 PDGFR α -negative and 7 PDGFR α -status unknown). One patient with unknown PDGFR α status achieved complete hematologic response, and two (one PDGFR α negative and one status unknown) achieved partial hematologic response. Our results confirm low response rate to imatinib in HES patients with unknown or negative PDGFR α status, and underscore the need for new therapeutic options for this disorder.

Keywords

Hypereosinophilic syndrome; imatinib; gleevec; tyrosine kinase inhibitor; FIP1L1–PDGFR α

Introduction

The hypereosinophilic syndrome (HES) defines a group of myeloproliferative neoplasms characterized by chronic eosinophil overproduction in the absence of obvious reactive or clonal causes of eosinophilia. Traditionally, a diagnosis of HES requires the presence of an absolute eosinophil count of $>1.5 \times 10^9/L$ for at least 6 months, which is associated with signs of organ involvement and dysfunction.(1-3) Chronic eosinophilic leukemia (CEL) is defined as eosinophilia associated with either a molecular or a cytogenetic clonal marker or the presence of peripheral blood blasts over 2% or bone marrow blasts over 5%.(4) Conventional therapy for HES customarily entails the use of corticosteroids, interferon alpha (IFN- α), and/or the use of cytoreductive agents such as hydroxyurea, vincristine or

cyclosporine.(5, 6) In recent years, distinct molecular and cytogenetic abnormalities have been identified in subsets of patients historically considered as having HES. These molecular abnormalities have brought about important taxonomic changes but also have resulted in the development of targeted therapeutics for patients with these disorders.(7-11)

Imatinib mesylate is a moderately potent, ATP-competitive tyrosine kinase inhibitor (TKI) highly active against the ABL, platelet derived growth factor (PDGFR) and KIT protein kinases.(12, 13) Encouraged by the impressive activity of imatinib in patients with chronic myeloid leukemia, imatinib was tried in patients with HES with good outcomes.(14-16) In 2003, Cools *et al* described a karyotypically occult but fluorescence *in situ* hybridization (FISH)-apparent molecular aberrancy in a subset of patients diagnosed as having HES.(8) This abnormality consisted of an interstitial deletion of chromosome 4q12, leading to the fusion of the FIP1-like 1 (*FIP1L1*) gene to the platelet derived growth factor- α (*PDGFR α*) gene. The resultant product, FIP1L1–PDGFR α , is a constitutively active tyrosine kinase highly amenable to inhibition by imatinib, thus providing the rationale for the use of imatinib in such patients.(8, 9) We used imatinib as a therapy for patients with HES for whom PDGFR α status was either unknown or negative and report our results here.

Materials and Methods

Patients with HES, defined according to established criteria, were included in this prospective single institution trial. Patients had to have symptoms and signs of the disease requiring therapy (indicating organ dysfunction; evidence of end-organ damage was not sought). Patients were allowed to enter the study on a stable dose of their current HES-directed medication (hydroxyurea or prednisone), provided its dose was stable for at least 4 weeks before study entry. Other inclusion criteria were Eastern Cooperative Oncology Group performance status ≤ 2 , total bilirubin level < 2 mg/dL, serum creatinine < 2 mg/dL, and NYHA class ≤ 2 . The protocol was approved by the Institutional Review Board of M. D. Anderson Cancer Center. All patients signed a written informed consent. The starting dose of imatinib was 100 mg orally daily. If no response was observed after 4 weeks or there was evidence for disease progression, the imatinib dose could be increased to 400 mg orally daily. Patients were followed by complete blood count and metabolic panel every 2-6 weeks for first 6 months and every 3-4 months thereafter. A bone marrow aspirate was performed after 3-4 months of therapy, and then every 3-6 months during the first 12 months. Complete hematological response (CHR) was defined as normalization of white blood cell (WBC) count with absolute eosinophil count (AEC) of less than $0.250 \times 10^9/L$ for ≥ 4 weeks.(17) Partial hematological response (PHR) was defined as $\geq 50\%$ decrease in baseline eosinophil count with AEC still greater than $0.250 \times 10^9/L$, lasting for ≥ 4 weeks.(17) Concomitant use of any other HES-directed therapy precluded response evaluation. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

Results

Between April 2002 and August 2005, 18 patients were enrolled (Table 1). Median number of prior therapies was 1 (range 0-4) but 7 patients received imatinib as frontline therapy. Prior therapies included prednisone (n=9), hydroxyurea (n=8), interferon- α (IFN- α ; n=4), cyclosporine (n=2), methotrexate (n=1), antithymocyte globulin (n=1) and subcutaneous

cytarabine (n=1). Since several patients entered the study on a stable dose of HES-directed medication (prednisone or hydroxyurea), the AEC might have been decreased at that point in time in these cases. Evaluation of bone marrow biopsy was compatible with HES in all patients, without the evidence for associated hematologic malignancy (including no evidence for mast cell infiltration). Seventeen patients had diploid cytogenetics, and one had inversion 9 (constitutional abnormality). FIP1L1-PDGFR α mutation status [tested by polymerase chain reaction (PCR)] was negative in 11 patients; 7 patients were not tested (stored tissue is not available for testing). All patients were negative by PCR for BCR-ABL rearrangement. Attempts to further subdivide patients in lympho- or myelo-proliferative variants were not undertaken: screening for an abnormal T-cell clone was not performed; immunoglobulin E and vitamin B12 were not measured; blood tryptase level was normal in 6 evaluable patients.

One patient achieved CHR. The patient was 41-year-old man previously treated with prednisone, IFN- α , and hydroxyurea. He complained of fatigue, gastroesophageal reflux, arthralgias and subcutaneous nodules. Liver and spleen were not enlarged. His WBC count was $10.1 \times 10^9/L$ with 36% eosinophils (AEC $3.6 \times 10^9/L$), hemoglobin 14.6 g/dl and platelet count $207 \times 10^9/L$. Bone marrow biopsy showed 22% eosinophils and normal karyotype. PDGFR α mutation status was not assessed. He received imatinib 100mg daily and achieved CHR in 3 weeks. He experienced complete resolution of his symptoms, and bone marrow at 3 month evaluation showed 3% eosinophils. Unfortunately, this patient died in a car accident, while in CHR for 16 months, on imatinib 100 mg/day.

Two patients achieved PHR with improvement in hypereosinophilia related symptoms. The first patient was a 59 year old male (previously untreated) who presented with asthma-like symptoms. His WBC count was $9.4 \times 10^9/L$, with 19% eosinophils (AEC $1.8 \times 10^9/L$). He was PDGFR α mutation negative. After 2 months of treatment with imatinib (required dose increase at 1 month from 100mg daily to 400mg daily of imatinib), his AEC decreased to $0.4 \times 10^9/L$, with significant improvement in symptoms lasting for 26 months. The second patient was a 72-year-old male who presented with shortness of breath, skin rash, pruritus and acid reflux, and was not responding to ongoing therapy with prednisone. His AEC was minimally elevated at $0.69 \times 10^9/L$ (PDGFR α mutation status not available). With imatinib treatment (requiring dose escalation at 1 month to 400mg daily), and while off prednisone, he achieved symptomatic improvement and >50% decrease in AEC, lasting for 8 weeks.

At present, only one patient is still receiving therapy on the study, taking imatinib 300 mg/day. At the start of the therapy, his AEC was minimally increased (AEC $0.44 \times 10^9/L$). He had frequent flu-like symptoms and skin rashes, despite ongoing therapy with high dose corticosteroids. He was FIP1L1-PDGFR α negative. He has been taking imatinib for 34 months, with his symptoms completely resolved and is off corticosteroids. His AEC has not changed with the imatinib treatment, however, and he has not fulfilled response criteria.

Other patients showed no response to imatinib treatment, even after dose escalation to 400 mg daily. Two patients were not compliant with prescribed therapy on the protocol. Overall, of the 11 patients with negative PDGFR α status, one patient achieved PHR, and of the 7 patients with unknown PDGFR α mutation status, one patient each achieved CHR and PHR

(Table 2). Imatinib was well tolerated with grade 3 neutropenia seen in 2/18 patients (11%) at 400mg daily dose of imatinib. Grade 3 non-hematological toxicity included diarrhea (n=2), fatigue (n=1), and weight gain (n=1). In 15 patients, the dose of imatinib was increased to 400mg daily due to no response (at 1 month in 14, and at 3 months in 1 patient). In 5 of those patients on 400mg daily, the dose had to be lowered due to side effects (final dose 300mg daily in 3, and 200mg daily in 2 patients).

Discussion

Here we report our experience with the use of imatinib as a therapy for HES patients for whom the PDGFR α status was either negative or unknown. It must be noted that at our institution we started treating patients with HES/CEL with imatinib before imatinib's approval in October 2006 by the United States Food and Drug Administration (FDA) for this indication. Expectations at the study initiation in 2002 were high (based on the discovery of FIP1L1-PDGFR α abnormality at that time), with hopes that imatinib would have benefited most patients with HES, which led us to enroll into the study 7 previously untreated patients. Since then the role of imatinib as therapy for HES/CEL has been clarified. Imatinib is approved for the treatment of adults with HES/CEL associated with the FIP1L1-PDGFR α mutation (recommended starting dose of 100 mg/day), and for patients with HES/CEL whose FIP1L1-PDGFR α status is negative or unknown (recommended starting dose of 400 mg/day). The efficacy of imatinib therapy for patients with eosinophilia carrying the FIP1L1-PDGFR α has been solidly established.(8, 17-25) Baccarani *et al* reported a CHR of 99% (72/73) in patients carrying FIP1L1-PDGFR α compared to 19% (13/69) in patients without this mutation.(17) Imatinib has therefore become standard of care for this subset of patients to the point that therapy with imatinib is recommended even in the absence of symptoms, to prevent the risk of end-organ damage. On these grounds, it is imperative to rule out, from the onset, the presence of PDGFR α rearrangement. A positive test would also give an opportunity to treating physician to use proper imatinib's dose, and to provide the patient with correct information regarding his/her prognosis. This is important since the degree and the quality of the response between PDGFR α -positive and -negative/unknown status patients is markedly different. Only rarely patients with true HES (i.e. lacking FIP1L1-PDGFR α) respond to imatinib, and when they do, response is usually limited to the improvement in symptoms. It is possible that the responses seen in these patients are the result of the presence of alternate imatinib-sensitive tyrosine kinase (e.g. PDGFR β). We were not able to evaluate this possibility in our patients due to lack of stored material. In the community setting, however, testing for alternate tyrosine kinase is largely not available and, therefore, our results likely reflect common experience in everyday practice.

In conclusion, therapy with imatinib for patients with HES should not be indiscriminate and should be based on the risk/benefit ration when compared to other available standard therapies. Corticosteroids remain the first choice therapy for HES patients. Further investigative efforts must be directed to the discovery of novel molecular targets and treatments for such patients.

Acknowledgements

The authors declare no conflict of interest. Contributions: N.J. and S.V. were responsible for all phases of the manuscript preparation and submission. J.C., A.Q., G.G., and H.K. contributed equally and were responsible for critical inputs and review of the draft and final version of the manuscript. T.M. and R.L. performed the molecular analysis and provided input into the manuscript preparation.

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Table 1

Baseline characteristics of the patients (n=18)

Characteristics	Median (Range)
Age, years	52.5 (26-77)
Males, number	10
Hemoglobin, g/dL	13.2 (7.7-15.2)
WBC count, $\times 10^9/L$	8.4 (5.2-41.3)
Platelet count, $\times 10^9/L$	233 (63-434)
Peripheral eosinophils, %	24 (6-50)
Peripheral absolute eosinophil count, $\times 10^9/L$	1.95 (0.44-12.39)
Marrow eosinophils, %	18 (5-28)
Prior disease duration, months	32 (6-252)
Prior therapies, number	1 (0-4)

Table 2Hematological response by PDGFR α mutation status (n=18)

PDGFR α mutation status	Response
PDGFR α Negative (n=11)	CHR = 0
	PHR = 1
PDGFR α Unknown (n=7)	CHR = 1
	PHR = 1

PDGFR α = Platelet derived growth factor- α , CHR = Complete hematological response, PHR = Partial hematological response