BRIEF REPORT
Congenital and Childhood Myeloproliferative Disorders With Eosinophilia Responsive to Imatinib

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Eosinophilia is seen in several myeloproliferative disorders (MPD). A subset of MPD involves the platelet-derived growth factor receptor beta (PDGFRB) gene. Imatinib mesylate has been efficacious in treating some of these MPDs. Here we describe two patients with MPD with eosinophilia and PDGFRB rearrangements, one of which was congenital. Both patients were treated with single agent imatinib and continue to be in clinical, hematologic, and cytogenetic remission despite weaning doses. No definite guidelines currently exist regarding the exact dosing and duration of imatinib therapy for these patients. Pediatr Blood Cancer 2012; 59:928–929. © 2012 Wiley Periodicals, Inc.

Key words: Imatinib; myeloproliferative disorders; PDGFRB

INTRODUCTION

Myeloproliferative neoplasms (MPN) include a spectrum of eosinophilic disorders [1,2]. Imatinib-sensitive mutations in bcr/abl-negative myeloid disorders have involved a subset of receptor tyrosine kinases (RTKs), including platelet-derived growth factor receptor beta (PDGFRB) [2], PDGFRA, and Kit. Reported clinical and laboratory features have included splenomegaly, leukocytosis, and eosinophilia in most patients and hepatomegaly, monocytosis, and skin involvement in some [3,4].

Only rare pediatric cases with PDGFRB associated MPN have been reported [5,6]. The youngest patient described was 5 months old at presentation. This infant had a balanced translocation t(1;5) (q21; 33) and no evidence of a constitutional abnormality [5]. Here we describe two patients with PDGFRB associated MPN responsive to imatinib therapy.

CASE REPORT

Case 1

A newborn male, born at 34 weeks gestation, was noted to have hepatomegaly and multiple purpuric nodular lesions over the entire body (Fig. 1A). Biopsy of a skin nodule showed myeloid proliferation with prominent eosinophilic infiltrate (Fig. 1B). At 1 month of age he was noted to have a WBC of 37.6 x 10^9/L with 10.1 x 10^9/L monocytes, 13.9 x 10^9/L neutrophils and 5.6 x 10^9/L eosinophils, hemoglobin 11.5 g/dl and platelets 133 x 10^9/L. He had no stigmata of Noonan syndrome or NF-1.

At the age of 3 months, he presented to our department, and was noted to have hepatosplenomegaly and persistent skin lesions. His height was less than 3rd percentile and weight in 3–10th percentile. Laboratory evaluation revealed a WBC of 86.7 x 10^9/L, hemoglobin 7.7 g/dl, platelet count of 40 x 10^9/L and 23% eosinophils. Bone marrow aspirate showed eosinophilia (21.1%) and monocytosis, but no blasts. He was initially started on hydroxyurea with slight improvement in WBC count. Chromosome analysis on patient’s peripheral blood sample revealed two cell lines with a t(1;5) (q21; 33), TPM3-PDGFRB in 64% of cells and a normal male karyotype in the other 36%. Fluorescence in-situ hybridization (FISH) on peripheral blood sample showed a 5q33 rearrangement involving the PDGFRB locus in 33% of cells.

He was started on imatinib at 340 mg/m^2/day at 4 months of age. After 1 week of therapy, the dose was reduced to 170 mg/m^2/day. With 1 month of imatinib, the patient had normal blood counts and a complete resolution of skin lesions and hepatosplenomegaly. Repeat FISH after 9 months of imatinib therapy showed no evidence of 5q33 rearrangement.

The patient is now 2 years old and on 92.5 mg/m^2 daily of imatinib. He is tolerating imatinib without side effects. His peripheral blood counts continue to be normal. He is 50–75th percentile for height and 25–50th percentile for weight.

Case 2

The patient is a 4-year-old male who suffered frequent respiratory infections and had symptoms of reactive airway disease since 7 months of age requiring 13 hospitalizations by the age of 3. By 18 months, he had failure to thrive and increasing abdominal girth. Examination revealed hepatomegaly, height at 6th percentile and weight at 39th percentile. CT chest (11 months) showed multifocal airspace consolidation and mediastinal lymphadenopathy. An esophageal biopsy showed rare intraepithelial eosinophils. At age 3, he had an ultrasound abdomen which showed hepatosplenomegaly, a liver biopsy revealed portal triaditis and increased eosinophils (Fig. 2). He has unilateral coloboma and a Type I laryngeal cleft.

He was referred to our department at age 4 at which time he had a WBC of 15.6 x 10^9/L, hemoglobin 12.5 g/dl, platelets 213 x 10^9, eosinophils 3.9 x 10^9/L, neutrophils 3.4 x 10^9/L, and monocytes 0.6 x 10^9/L. Bone marrow showed marked eosinophilia (18.8%), and no blasts. FISH analysis revealed 5q33 rearrangement involving PDGFRB locus in 6.5% cells. Due to...
this disorder. Of note, our patient with congenital disease [5,6]. There has been no report of a congenital presentation of PDGFRB rearrangement and eosinophilia have been reported [8]. With respect to case 2, the resolution of chronic lung disease after the initiation of imatinib suggests that this patient’s pulmonary symptoms were also related to his neoplasm.

Now at 4.5 years of age, he is at 10th percentile for height and 49th percentile for weight. Adjusting for his current body surface area, he is on 145 mg/m²/day of imatinib. His peripheral counts continue to be normal. His most recent CT scan shows decreased ground glass opacity and resolution of hilar lymphadenopathy.

DISCUSSION

Myeloid neoplasms associated with the PDGFRB rearrangement represent a small subset of primary eosinophilia. The disease is more frequent among males with a peak incidence between 25 and 55 years. Clinical presentation of eosinophilia varies from asymptomatic eosinophilia to life-threatening cardiac or neurological complications [7]. Although rare in children, idiopathic eosinophilia can occur in children of all ages, typically with less of a male predominance than in adults, and with the most common presenting symptoms being fever, arthralgia, fatigue, and rash [8]. With respect to case 2, the resolution of chronic lung disease after the initiation of imatinib suggests that this patient’s pulmonary symptoms were also related to his neoplasm.

Only a few pediatric cases of this myeloid neoplasm with PDGFRB rearrangement and eosinophilia have been reported [5,6]. There has been no report of a congenital presentation of this disorder. Of note, our patient with congenital disease demonstrated TPM3 as the fusion partner of PDGFRB, which is quite rare, particularly in the pediatric population [9,10]. Both patients we described achieved cytogenetic remission within 1 month following initiation of imatinib therapy. They attained hematologic and clinical remissions within 3 months and remained in remission despite weaning doses of imatinib.

Appropriate imatinib starting and maintenance doses remain unclear for the pediatric population with this rare myeloproliferative disorder (MPD), although a dose of 400 mg/day has been recommended for their adult counterparts. The maintenance level required to maintain continuous remission varies among patients and molecular testing is the most useful method of determining the optimal dosage [11,12]. Our experience with these two cases suggests that at least a subset of patients with MPD with PDGFRB rearrangement may be dosed well below the standard 340 mg/m².

The long-term prognosis of our patients is, at present, uncertain. Undiagnosed, this condition can be long standing. In general, in an imatinib responsive patient without end-organ damage, the outlook is favorable, and cases of acquired imatinib resistance appear to be rare. The long-term administration of a tyrosine kinase inhibitor may have adverse outcomes and concerns regarding possible cardiac toxicity, alteration of bone turn-over, growth, and glucose metabolism have been raised [12]. This highlights the need for careful monitoring of these patients and the use of the lowest effective dose of imatinib. The ideal duration of imatinib therapy for these patients is unknown. For this reason, identifying fusion partners and developing a PCR based assay to evaluate for minimal disease can be helpful, particularly when lowering the dose or discontinuing imatinib.

Despite the above uncertainties in treatment of pediatric MPN with eosinophilia and PDGFRB abnormalities with imatinib, it is clear that accurate molecular diagnosis of PDGFRB rearrangements is necessary before choosing a targeted therapy [13]. A recent article reported the development of a universal method for detection and validation of all possible PDGFRB fusions in patients [9]. Similar assays might be valuable in identification of patients with MPN and eosinophilia harboring PDGFRB fusion.

REFERENCES