



A Mini Review

Chronic Eosinophilic Leukemia: A Mini-Review

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Introduction

Eosinophilia has been defined as an absolute eosinophil count of more than 500 eosinophils/mm³ of venous blood [1]. In patients with marked eosinophilia (>1,500 eosinophils/mm³) which persisted for more than six months, the working conference on eosinophil disorders and syndromes proposed in 2011 a new classification [2]. Hypereosinophilia (HE) was classified as familial, undetermined significance, primary clonal or neoplastic and reactive; when associated with end organ damage it should be classified as Hypereosinophilic Syndrome (HES).

The majority of cases are secondary or reactive, in developing countries most commonly due to infections, especially tissue invasive parasites [3]. Reactive eosinophilia to other tumors, allergy or collagen vascular disease needs to be excluded. The age adjusted incidence for HES is of the order of 0.036 cases/100,000 population, of which Chronic Eosinophilic Leukemia (CEL) comprises a minority of these patients [4].

In 2008, the WHO revised the classification of eosinophilia in myeloid neoplasms, creating a new category; myeloid and lymphoid neoplasms with eosinophilia and abnormalities of Platelet Derived Growth Factor Receptor Alpha (PDGFRA), Platelet Derived Growth Factor Receptor Beta (PDGFRB) or Fibroblast Growth Factor Receptor 1 (FGFR1) [5].

There are two forms of Chronic Eosinophilic Leukemia (CEL) the CEL FIP1L1-PDGFRB rearrangement positive, which is part of the new subcategory of the WHO classification and the CEL-NOS (not otherwise specified) which forms part of the myeloproliferative neoplasms of the WHO classification [6].

CEL is a chronic myeloproliferative disease with a clonal proliferation of eosinophilic precursors. This results in a persistently elevated number of eosinophils in the blood, bone

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marrow and peripheral tissues [7]. The WHO proposed diagnostic criteria for CEL include: a persistent eosinophilia of $\geq 1.5 \times 10^9/L$ in peripheral blood persisting for more than 6 months and increased bone marrow eosinophilia with between 5-19% of myeloblasts in bone marrow samples or >2% in the peripheral blood and clonality of the myeloid cells should be demonstrated [7]. The etiology of CEL is unknown, although two cases associated with occupational or therapeutic radiation exposure have been reported [8]. The available evidence suggests that its incidence is highest in the fourth decade. Differing from other causes of hypereosinophilia where there is no clear gender difference, CEL NOS is more common in males with a ratio of 1.47, whereas CEL FIP1L1-PDGFRB patients are in the majority of cases male and in almost all cases there is clinically palpable splenomegaly [9].

The disease has been characterized by a chronic phase that may progress to a blast crisis. Historical case series reported a high mortality, with a 12 year survival of only 12%, the majority presenting in advanced stages and the dying of cardiac disease caused by the hypereosinophilia [9]. However in the era of molecular defined eosinophilias, improved and earlier diagnosis, the use of targeted therapy and cardiovascular surgery the survival has improved [9].

The neoplastic nature of CEL has been substantiated by a number of chromosomal abnormalities, the most frequent being trisomy 15, trisomy 8, isochromosome 17, translocations t(2;5)(p23;q31) and translocations t(5;12)(q33;p13) [10-14].

At the molecular level CEL has been divided into two entities, which has important therapeutic implications.

Chronic eosinophilic leukemia FIP1L1-PDGFRB rearrangement positive: The FIP1L1-PDGFRB rearrangement is caused by a cryptic deletion of 800kb on chromosome 4q12 and contains the CHIC2 gene [15], the incidence of this entity as part of the HES is not known, those with fusion protein rearrangements are very rare, estimated to be <1/100,000 persons with HES. The original work of Cools et al., [16] reported 56% of patients were FIP1L1-PDGFRB positive, however in those series with more than 10 patients with HES, the incidence of CEL FIP1L1-PDGFRB ranges from 3% to 56% [9]. Although these studies have selection bias, the incidence of patients positive for FIP1L1-PDGFRB is probably between 10-20% of patients presenting with HES in developed countries.

Fusion of FIP1L1 to the PDGFRB protein yields a constitutive active tyrosine kinase which stimulates the proliferation and mediates survival of the eosinophils in CEL patients, through activation of several signaling pathways including phosphoinositide-3-kinase, ERK 1/2 and STAT5 [17,18]. The exact mechanism, however, by which FIP1L1-PDGFRB preferentially affects eosinophils, remains unclear.

FIP1L1-PDGFRB is a clonal marker associated with the myeloproliferative variant of hypereosinophilia [17,19]. These patients often present with organomegaly, a hypercellular bone marrow with increased mast cells and/or myelofibrosis and increased serum tryptase levels.

The use of low dose imatinib (100-400mg/day) produces complete and rapid hematological remissions and normalization of peripheral blood and bone marrow eosinophilia, with a median time to response of four weeks [20]. Molecular remissions, with patients becoming RT-PCR negative for FIP1L1-PDGFR A occurring after a median of 3 months [20,21]. However, discontinuation of imatinib can rapidly lead to relapse [17,22], with molecular remission being achieved following its reintroduction. A single weekly dose of 100-200mg of imatinib may be sufficient to maintain remission [18].

Acquired resistance to imatinib is much less frequent in patients with CEL FIP1L1-PDGFR A than that observed in CML patients. It is associated with the T674I mutation within the ATP binding domain of PDGFR A and may be seen in patients developing a blast crisis. The T674I confers broad spectrum resistance to tyrosine kinase inhibitors nilotinib, sorafenib [23], and dasatinib [23], ponatinib a pan-FIP1L1-PDGFR A inhibitor has shown *in vitro* activity in cells expressing the T674I mutation [24].

Chronic eosinophilic leukemia-NOS: CEL-NOS is operationally defined by; an absolute peripheral eosinophilia count of $>1.5 \times 10^9/l$; there is no philadelphia chromosome or BCR-ABL fusion gene detectable, is not part of another myeloproliferative neoplasms (polycythemia vera, essential thrombocytosis; myelofibrosis or systemic mastocytosis) or a myelodysplasia/myeloproliferation syndrome (CMML or atypical CML); there is no t(5;12) or other rearrangement of PDGFR B; there is no FIP1L1-PDGFR A fusion gene or other rearrangement of PDGFR A; there is no rearrangement of FGFR1 and finally the blast cell count in the peripheral blood is less than 2% and in the bone marrow is between 5% and 20% and there is no inv(16)(p13;q22) ort(16;16)(p13;q22) or other feature diagnostic of AML [6].

In cases of CEL where the RT-PCR for FIP1L1-PDGFR A is negative or unknown, the prognosis is poor, being unresponsive or short lived to imatinib [25], conventional therapy [26] and has a high rate of acute transformation [26]. However, it has been reported that approximately 40% of patients who response to imatinib are negative for the FIP1L1-PDGFR A fusion protein, although doses as high as 600mg/day may not be effective [27]. The complete response rate has been reported as 24% compared with 98% of cases which were FIP1L1-PDGFR A positive [16]. However, hematological responses are often partial and short lived [26].

However, high doses of imatinib may not be tolerated, with grade 3 or 4 leukopenia, neutropenia, lymphopenia, trombocytopenia and anemia being reported in between 3 and 8% [20]. Fluid retention may require the use of diuretics and nausea and diarrhea may be sufficient to withhold therapy in 4% of patients [28].

Nevertheless the prognosis of CEL-NOS is poor in a cohort of 10 patients; the median survival was 22.2 months, with acute transformation occurring in 5 of the 10 patients [26].

Conclusion

In patients with eosinophilia, the presence of the FIP1L1-PDGFR A mutation is an indication for low dose imatinib and implies an excellent prognosis, though long term therapy is required. Those complying with the diagnostic criteria of CEL but are FIP1L1-PDGFR A negative, may warrant a trial of higher dose imatinib.

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