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FMS-like Tyrosine Kinase 3 (FLT3) Gene as a Significant Biomarker for Acute Myeloid Leukemia

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ABSTRACT

Acute myeloid leukemia (AML), a cancer of myeloid cells involves the abnormal proliferation and differentiation of myeloid stem cells. AML accounts for approximately 30% of leukemia's but >40% of leukemia-related deaths. AML is highly diverse and cytogenetic analysis of metaphase cells reveals that approximately 40-50% of patients with de novo AML have a normal karyotype.. This study demonstrated activating mutations of FLT3 gene due to recent advances in cell and molecular biology have revolutionized our understanding of normal hematopoiesis. Mutations within the FMS-like tyrosine kinase 3 (FLT3) genes represent one of the most frequently identified genetic alterations that disturb intracellular signaling networks with a key role in leukemia pathogenesis. The present study has been designed to highlight and signify the importance of FLT3 and its related gene mutations involved in the onset and progression of Leukemias. Since mutations in FLT3 gene are one of the most common clinically relevant mutations which are expressed in 90% of leukemic blasts of patients with acute myeloid leukemia. Thus, there is an urgent need for the better understanding of the key genetic mutations involved in disease progression and prognosis. FLT3 testing should be done in parallel with cytogenetic testing and can open new horizons for better diagnosis and better treatment option.

KEY WORDS: ACUTE MYELOID LEUKEMIA, FMS-LIKE TYROSINE KINASE, GENETIC MUTATIONS.

INTRODUCTION

Leukemias are monoclonal diseases that originate from individual cells in the bone marrow. Leukemia like any other cancer also follows a multistep process which a normal cell must possess or pass through a number of distinct intermediate stages before attaining the status of malignancy. Based on the origin of the predominant cell type (myeloid or lymphoid) and the rate of disease progression (acute or chronic), leukemia is categorized into four major subtypes: acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL). According to a recent report published by Taisen et al., (2019), the incidences of AML and CML has remained constant prior to 2011 but there has been a sudden increase in the incidence rates of CLL. Acute myeloid leukemia (AML), a cancer of myeloid cells involves the abnormal proliferation and differentiation of myeloid stem cells. It is generally accepted that survival, proliferation and differentiation are the three fundamental cellular processes that define normal hematopoietic cells. In acute myeloid leukemia

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(AML), a heterogeneous disorder of the hematopoietic progenitor cells, abnormalities have been identified that affect the balance between cell proliferation, survival and differentiation. These abnormalities result in the expansion of an abnormal stem cell clone (Irons et al., 1996 Taisen et al., 2019 Nicholas et al 2020).

AML accounts for approximately 30% of leukemia's but >40% of leukemia-related deaths. It is the most common acute leukemia in adult population. The median age at diagnosis of AML is approximately 67 years and about 1/3rd of Leukemias among adults have been reported from developed countries. The therapeutic armamentarium of acute myeloid leukemia (AML) has rapidly expanded in the past few years, driven largely by translational research into its genomic landscape and an improved understanding of mechanisms of resistance to conventional therapies (Nicholas et al., 2020). Genetic alterations are the frequent features of all human cancers which include amplification, deletions, rearrangements and point mutations. Thus, genomic investigations of AML have also demonstrated the role of several genes which on recurrent mutations can lead to the new genomic classifications and predictive biomarkers, and new therapeutic targets (Daver et al., 2019 Nicholas et al 2020).

AML is highly diverse and cytogenetic analysis of metaphase cells reveals that approximately 40-50% of patients with de novo AML have a normal karyotype. These patients are classified with an intermediate clinical prognosis because clinically they do not have a reference marker and its biological origin is still unknown. The most frequent abnormalities are translocations t(15;17), t(8;21), inv(16) and a gain of number 8. Recently, with the development of methodologies of massive sequencing, new genetic mutations associated with acute myeloid leukemia have been identified. Some of the identified genes include KIT, FLT3, NPM1, CEBPA, RAS, WT1, BAALC, ERG, MN1, DNMT, TET2, IDH, ASXL1, PTPN11 and CBL. Of all these, WHO highlighting the related mutations in FLT3, NPM1 and CEBPα genes because they are associated with treatment response and progress of this disease (Swerdlow et al., 2008, Takahashi 2011, Martelli 2013 and Liesveld and Lichtman, 2016, Rubnitz et al., 2016 Nicholas et al 2020).

A number of genetic mutations, such as point mutations, gene rearrangements, and chromosomal translocations, which are involved in the pathogenesis of leukemia, have been documented. Recent advances in cell and molecular biology have revolutionized our understanding of normal hematopoiesis. Mutations within the FMS-like tyrosine kinase 3 (FLT3) genes represent one of the most frequently identified genetic alterations that disturb intracellular signaling networks with a key role in leukemia pathogenesis. FLT3, a receptor tyrosine kinase (RTK), is a membrane-bound receptor is primarily expressed on committed myeloid and lymphoid progenitors. FLT3 is composed of an immunoglobulin-like extracellular ligand-binding domain, a transmembrane domain, a juxtamembrane dimerization domain and a highly conserved intracellular kinase domain interrupted by a kinase insert. FLT3 belongs to the class III subfamily of RTKs, which include structurally similar members such as c-FMS, c-KIT, and PDGF receptor (Martelli et al, 1996 and Gabbianelli et al., 1995 Liesveld and Lichtman 2016).

FLT3 is expressed in 90% of leukemic blasts of patients with acute myeloid leukemia (Carow et al.,1996) . Approximately 20–30%ofAMLpatientsharbor a unique feature i.e. Internal Tandem Duplication (ITD) mutation in the FLT3 gene between exons 14 and 15 in the juxta membrane domain, which often results in high blast accounts, increased risk of relapse and decreased survival. FLT3-ITD is especially a frequent feature in patients with normal karyotype, t (15;17) (q22;q12) [PML-RARA] and t(6;9)(p23;q34) [DEK-NUP214]which leads to uncontrolled cellular proliferation, survival, and differentiation through constitutive activation of FLT3, (Meshinchi and Appelbaum (2009). Stirewalt and Radich 2003, Parcells et al, 2006) .FLT3-ITD occurs in the form of a replicated sequence in the juxta membrane domain and/or TKD1 of the FLT3 receptor and varies in location and length within these domains.

FLT3-ITD (high) is a driver mutation that presents with a high leukemic burden, confers a poor prognosis, and bears a significant negative impact on the management of patients with AML (Ding et al., 2012, Grimwade and Mrozek 2011). This ITD disrupts the auto inhibitory function of the juxta-membrane domain and results in ligand independent activation of the FLT3 receptor. This leads to a proliferative signal via activation of its downstream effectors (Kiyoi et al., 1998, Levis 2013) . Thus, the ITD leads to gain of function mainly by inducing hyper-responsivity of the FLT3 receptor to FL rather than through auto-activation of the receptor (Griffith et al., 2004), Therefore, the FLT3-ITD mutation directly or indirectly confers a selective advantage to a clone in its microenvironment. About 75% of patients with FLT3ITD–mutated AML at diagnosis continue to have the ITD mutation at relapse (Zheng et al., 2011) suggesting that FLT3-ITD may function as the driver mutation responsible for progressing the disease into overt leukemia.

The second common types of mutations in FLT3 are missense mutations in exon 20 of the activation loop (A-loop) in the tyrosine kinase domain (TKD). Almost all these mutations involve the substitution of an aspartate with a tyrosine at codon 835 (D835Y) by a point mutation (GAT→TAT). Aspartate in the 835 position belongs to the domain DFG (Aspartate-Phenylalanine-Glycine) in the A-loop, playing a critical role in preventing efficient binding of ATP. This type of mutation occurs in approximately 7% of patients with AML (Yomamoto et al., 2001 Kronke et al., 2013 Liesveld and Lichtman (2016).

In recent years, it has been shown that somatic activating mutations of the FLT3 gene are the most common genetic abnormalities in AML and have a significant impact on prognosis. Female patients are affected more

frequently and these mutations are also associated with hypercellularity and a higher incidence of recurrence (Abu- Duhier et al., 2001). Routine testing for FLT3 in patients with cytogenetically normal AML had been recommended since at least 2010 (Fenski et al., 2000), which corresponds to the time at which molecular testing was routinely performed in 100% of patients at academic centers but not at community sites. This suggests that there is a lack of awareness about the significance of molecular testing at community sites.

CONCLUSION

Identification of FLT3 mutations in AML has yielded novel approaches to the management of this disease. Over the last decade, the biology and the function of the wild-type and mutated FLT3 receptor have been well characterized. Whether it is through their utility as prognostic factors or their use as a target for directed therapies, FLT3 mutations have provided clinicians with novel therapeutic options for a large subset of AML patients. Identification of FLT3 mutations in AML has raised the potential for its utility as a molecular marker for risk-based therapy and as a target for directed therapy with novel small molecular inhibitors. Subsequent studies identified numerous other potential compounds (MLN518, PKC412, SU5416, SU5614, SU11248, CEP-701, CEP-5214) that also block FLT3 activation. Two compounds (CEP-701 and PKC-412) have shown some therapeutic promise for AML patients with FLT3 mutations. CEP-701 (Lestaurtinib) is an indolo carbazole compound that inhibits auto phosphorylation of the WT and mutant FLT3 receptors (Levis et al., 2005 and Levis et al., 2004, Nicholas et al 2020). Current clinical trials are combining FLT3 inhibitors with conventional chemotherapy in an attempt to increase the cytotoxic effect against leukemia cells and reverse the poor prognosis for AML patients with FLT3 mutations.

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