Approaches of chronic myelogenous leukemia.

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Abstract

Modern clinical therapy of chronic myeloid leukemia with TKIs is highly efficacious in most CML patients, while it is not remedial and generally confined due to intolerance or resistance. CML is currently considered a severe disease. Interestingly, stem cell transplantation in the past decade was an attractive clinical therapeutic option in CML patients, but it is not successful due to independently more death rates in older patients. So, the targeting of BCR::ABL oncoprotein is extensively used to enhance the reduction in a higher percentage of CML patients by tyrosine kinase inhibitors.

Keywords: Chronic myelogenous leukemia, Leukemia, Chromosomal translocation

Introduction

CML was the first cancer to be linked to a clear genetic abnormality, the chromosomal translocation known as the Philadelphia chromosome. This chromosomal abnormality is so named because it was first discovered and described in 1960 by two scientists from Philadelphia, Pennsylvania, USA: Peter Nowell of the university of pennsylvania and David Hungerford of fox chase cancer center [1].

Parts of two chromosomes (the 9th and 22nd) switch places. As a result, part of the BCR ("breakpoint cluster region") gene from chromosome 22 is fused with the ABL gene on chromosome 9. This abnormal "fusion" gene generates a protein of p210 or sometimes p185 weight (p210 is short for 210 kDa protein, a shorthand used for characterizing proteins based solely on size). Because abl carries a domain that can add phosphate groups to tyrosine residues (a tyrosine kinase), the bcr-abl fusion gene product is also a tyrosine kinas [2].

The fused BCR-ABL protein interacts with the interleukin 3beta(c) receptor subunit. The BCR-ABL transcript is continuously active and does not require activation by other cellular messaging proteins. In turn, BCR-ABL activates a cascade of proteins that control the cell cycle, speeding up cell division. Moreover, the BCR-ABL protein inhibits DNA repair, causing genomic instability and making the cell more susceptible to developing further genetic abnormalities [3].

The action of the BCR-ABL protein is the pathophysiologic cause of chronic myelogenous leukemia. With improved understanding of the nature of the BCR-ABL protein and its action as a tyrosine kinase, targeted therapies (the first of which was imatinib) that specifically inhibit the activity of the BCR-ABL protein have been developed. These tyrosine kinase inhibitors can induce complete remissions in CML, confirming the central importance of bcr-abl as the cause of CML [4].

CML is often suspected on the basis of a complete blood count, which shows increased granulocytes of all types, typically including mature myeloid cells. Basophils and eosinophils are almost universally increased; this feature may help differentiate CML from a leukemic reaction. A bone marrow biopsy is often performed as part of the evaluation for CML, and CML is diagnosed by cytogenetic that detects the translocation t(9;22)(q34;q11.2) which involves the ABL1 gene in chromosome 9 and the BCR gene in chromosome 22. As a result of this translocation, the chromosome looks smaller than its homologue chromosome, and this appearance is known as the Philadelphia chromosome chromosomal abnormality. Thus, this abnormality can be detected by routine cytogenetic, and the involved genes BCR-ABL1 can be detected by fluorescent in situ hybridization, as well as by PCR [5].

Conclusion

CML is often divided into three phases based on clinical characteristics and laboratory findings. In the absence of intervention, CML typically begins in the chronic phase, and over the course of several years progresses to an accelerated phase and ultimately to a blast crisis. Blast crisis is the terminal phase of CML and clinically behaves like an acute leukemia. Drug treatment will usually stop this progression if started early. One of the drivers of the progression from chronic phase through acceleration and blast crisis is the acquisition of new chromosomal abnormalities in addition to the philadelphia chromosome.

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