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شبكة المعلومات الجامعية

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التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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بالرسالة صفحات
لم ترد بالأصل

Diagnostic and Prognostic Significance of Deletion 20q12, Trisomy 8 and Trisomy 9 in cMPDs Patients

Thesis

Submitted for Partial Fulfillment of M.D. Degree in Clinial and Chemical Pathology

Presented By

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INTRODUCTION:

The chronic myeloproliferative disorders (cMPDs) are a group of disorders defined by proliferation of one or more lineages of the myeloid and erythroid series. This includes chronic myeloid leukemia (CML), polycythemia rubra vera (PRV), idiopathic myelofibrosis (MF), undifferentiated MPD and essential thrombocythemia (ET). With the exception of CML, chromosomal abnormalities are seen in 30%-40% of patients, although rarely in ET. Although, there is no pathognomonic chromosomal abnormality associated with these disorders, cytogenetic investigation is important to rule out Ph-positive CML ***(Harrison, 2005)***.

It is now well established that CMPDs share a common stem cell-derived clonal heritage and their phenotypic diversity is attributed to different configurations of abnormal signal transduction, resulting from a spectrum of mutations affecting protein tyrosine kinases or related molecules ***(De Keersmaecker and Cools., 2006; Tefferi and Gilliland., 2007)***. In principle, therefore, histology-based classification and diagnostic criteria for these disorders can be refined by employing molecular disease markers such as BCR-ABL fusion gene [t(9;22)(q34;q11)] and L3MBTL gene (20q12) ***(Tefferi and Vradiman., 2007)***.

The human L3MBTL gene is located in 20q12, a region that is commonly deleted in CMPDs, myelodysplastic syndromes (MDS), and acute myeloid leukemia (AML). L3MBTL is highly homologous to the D-lethal (3) malignant brain tumor [D-1(3)mbt] gene, which is a putative tumor-suppressor gene (TSG) identified in Drosophilia ***(MacGrogan et al., 2004)***.

In addition to deletion 20q12, some consistent chromosomal abnormalities have been described, including del (20)(q11), trisomy8, trisomy9, del(13)(q13-q31) and partial trisomy 1q, which seem to be associated with a poor prognosis. Frequently, the detection of a chromosomal abnormality in these cases is the only way to distinguish a malignant clone from a non-malignant hyperplasia ***(Harrison, 2005)***.

Molecular techniques such as fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), comparative genomic hybridization (CGH) and micrroarray coupled with conventional cytogenetic analysis (CCA), are used in many studies to clarify normal and oncogenic function of proto-oncogenes and tumor suppressor genes with high sensitivity and specificity in order to study their association with pathogenesis of CMPDs ***(Bench et al., 2005)***.

Recently, interphase fluorescence in situ hybridization (FISH) on granulocytes has been shown to be useful in recognizing MPD karyotypic abnormalities that have not been found by conventional karyotypic analysis ***(Gorusu et al., 2007)***.

Aim of the Work:

- Detection of deletion 20q, trisomy 8 and trisomy 9 by FISH technique coupled with CCA in cMPD patients.
- Evaluation of the diagnostic utility of such chromosomal abnormality in distinguishing malignant clone from non-malignant hyperplasia.
- Assessment of prognostic significance of these cytogenetic aberrations on patients' outcome.