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The Influence of N-RAS Gene Mutations on the Response to Induction Therapy in AML Iraqi Patients

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Abstract

Background N-RAS mutations are the most commonly detected molecular abnormalities in hematologic malignancies, especially in those of myeloid origin.

Objective Current study aimed to determine the frequency of N-RAS mutation; and its influence on response to induction therapy in patients with acute myelogenous leukemia (AML) in Iraq.

Methods Peripheral blood and bone marrow samples were taken from 58 newly diagnosed AML patients and 30 individuals with reactive bone marrow were selected as a control group. Samples screened for N-RAS gene mutations using nested PCR were followed by mutation sensitive digestion analysis (MSDA).

Results N-RAS mutations at the time of diagnosis were found in 10/58 (17.24%) patients with AML and no mutation in control individuals. Patients with mutant N-RAS showed lower complete remission (CR) than wild type, the difference was not significant (60% vs. 72.92%, $P = 0.414$).

Conclusion The current results provide clues for activation of RAS-signaling cascade in AML patients, supporting their role in molecular pathogenesis of leukemia. N-RAS mutations show no influence on CR rate in AML patients. Further studies on larger scale to define the prognostic significance of N-RAS mutations are recommended.

Keyword AML, N-RAS mutation, MSDA, complete remission.

Introduction

RAS proteins are small GTPases that act as molecular switches, transducing extracellular signals from activated receptors at the cell surface to the nucleus, thus, regulating cell proliferation, survival, and differentiation. Three RAS genes encode 4 widely expressed isoforms: H-RAS, N-RAS, and the splice variants K-RAS4A and K-RAS4B [(1)].

The RAS proteins possess intrinsic GTPase activity (induced hydrolysis of GTP to GDP), which normally leads to their inactivation and the control signal transduction. In tumors, a point mutation resulting in loss of the intrinsic GTPase activity and RAS proteins lock in an active state, does not stop anymore to send signal stimulating cell proliferation and appears to be associated with transforming activity of the protein. All RAS mutations were missense point mutations occur at codons 12, 13 (exon 1) and 61 (exon 2) [(2,3)]. Activating mutations of N-RAS are most common among myeloid malignancies, found in approximately 20% to 40% of myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic