RAS Oncogene Mutations are Rare Late Stage Events in Chronic Myelogenous Leukemia

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DNA from bone marrow and peripheral blood samples of 44 chronic myelogenous leukemia (CML) patients were analyzed for the presence of mutations of codons 12, 13 or 61 of the N-ras, H-ras, or K-ras genes. In seven patients, samples were available from both their chronic phase and blast crisis. A total of 29 samples examined were at chronic phase and 22 were at blast crisis (eight lymphoid, eight myeloid, and six undifferentiated). No mutations were identified in N-ras or H-ras. Two patients in myeloid blast crisis had K-ras mutations, one patient at codon 12, the other at codon 13. In the former patient the mutation was not present and the latter patient was not tested in chronic phase. Our findings indicate ras mutations are an infrequent late stage event in CML that occur in myeloid blast crisis.

RESULTS

Forty-four patients demonstrated only wild type sequences for N-ras with no codon 12, 13, or 61 mutations. The HL-60 control demonstrated both wild type and mutated (codon 61, CTA) sequences, as has been previously described (Fig 1A).3

Mutant K-ras sequences were identified in two of the 44 patients studied. Both patients were in myeloid blast crisis and demonstrated both wild type and mutant sequences. The first patient had a K-ras codon 12 substitution valine (GTT) for glycine (GGT) (Fig 1B). A sample obtained during chronic phase of this patient was normal for K-ras, H-ras, and N-ras. The second patient had a K-ras codon 13 substitution aspartic acid (GAC) for glycine (GCG) (Fig 1B). Unfortunately, no chronic phase sample was available in this patient for study. The SW480 control as reported was absent on the wild type screen with only sequences for a K-ras codon 12 mutation (GTT) (Fig 1B).4 The remaining 42 patients were normal for codons 12, 13, and 61 with no evidence of mutations.

No mutations were identified in the 44 patients studied for H-ras codon 12, 13, or 61. All of the patients demonstrated only wild type sequences.

DISCUSSION

Recent studies using PCR and SSO probe hybridization to ras amplified DNA in acute myeloid leukemias indicate that approximately 20% have mutated ras genes.3,10,11 In solid tumors such as colon and pancreatic carcinoma, the incidence ranges from 40% to 97%.12-14 The incidence in CML of mutations has ranged from none to 33% of patients studied.

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with most of the mutations found in blast crisis.4 The incidence in our study indicates that it is a relatively infrequent event since only two of the 44 patients (4%) had a ras mutation.

Our findings do support that concept that ras mutations occur as a late event in CML.4 Of the six cases with mutations that have been reported in this study and the literature, 5 five have occurred in blast crisis patients and our data suggest that they tend to occur in myeloid blast crisis. Furthermore, our findings of a K-ras codon 12 mutation at blast crisis when it was not present during chronic phase suggests that ras mutations may be a late event in some CML patients. Unfortunately, no other studies have examined serial samples and the lineage of the other patients reported with mutations is not known.

The finding of ras mutations as a late event in CML is different from those in carcinoma and myelodysplasia (MDS). A recent colon carcinoma study by Vogelstein et al suggested that while ras mutations may not be part of the first genetic alterations to occur during the development of colorectal tumors, they often were early events in tumorigenesis.13 These findings are consistent with those in MDS where ras mutations appear to be a relatively early event and may serve as a marker for progression to leukemia.515 An understanding of the biologic significance of ras mutations and their role in carcinogenesis and disease progression will be aided by delineating the genetic events which produce them.

REFERENCES


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