CML 01

DIAGNOSTIC VALUE OF C-ABL AND BCR SEQUENCES IN HUMAN LEUKEMIAS

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Molecular hallmark of Ph'-positive CML is a genomic rearrangement between sequences of the human c-abl oncogene and a gene of yet unknown function, called bcr. As a consequence of this recombination, leukemic cells express a novel c-abl/bcr hybrid transcript, the mRNA for an altered c-abl protein.

Sequences of both genes were used to investigate Ph'-positive ALL and Ph'-negative CML patients. Our results demonstrate heterogeneity within both leukemic subgroups. An analysis of 18 Ph'-positive ALL patients revealed a c-abl/bcr rearrangement indistinguishable from Ph'-positive CML in 8 cases; these patients may in fact suffer from CML initially diagnosed in blast crisis. Leukemic cells of other patients show a bcr rearrangement, but lack rearranged 3'bcr sequences normally transferred to chromosome 9q+, while in yet another subgroup of Ph'-positive ALL there is no bcr rearrangement at all.

As to Ph'-negative CML, most patients exhibit no c-abl or bcr activation. However, a subset of cases could be reclassified to the clinical entity of Ph'-positive CML by using molecular instead of cytogenetic approaches. Moreover, in a unique patient a bcr rearrangement and a novel bcr transcript could be demonstrated, while c-abl sequences were not involved in this genomic alteration.

Finally bcr sequences were used as a molecular marker for the early diagnosis of relapse in Ph'-positive CML following bone marrow transplantation.

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CML 02

MOLECULAR CHARACTERIZATION OF HUMAN LEUKEMIA: GENOTYPING OF LYMPHOID MALIGNANCIES WITH IMMUNOGLOBULIN AND T-CELL RECEPTOR GENE PROBES AND APPLICATION OF A bcr-SPECIFIC PROBE IN THE CLASSIFICATION OF CHRONIC MYELOGENEOUS AND ACUTE LYMPHOBLASTIC LEUKEMIAS

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We have studied the applicability of using DNA probes for determination of lineage and clonality of human lymphoid malignancies. Our data indicate that only B-cells have rearranged κ- and λ chain genes, whereas rearrangement of IgH chain genes can also occur in T-cells. T-cell related malignancies are characterized unequivocally by rearranged α-chain genes, whereas the ß-chain gene complex can also be rearranged in B-cells. The characterization of clonal expansion requires at least 5-10% of the malignant clone in the studied material.
We have also used a bcr-specific fragment as a probe for clonality in CML patients. Our data of multiple bcr-rearrangements in individual patients indicate that such rearrangements can occur independently and more than once in both myeloid and lymphoid lineages of individual patients. This suggests an apparent multi-clonality in CML patients with respect to bcr-rearrangements. The observation of bcr-rearrangements in acute leukemia indicates that this process is not restricted to CML.
We have studied the prevalence of common and rare alleles of the c-Ha-ras-1 locus in leukemia patients. Our data indicate that there is an at least five-fold higher prevalence of rare alleles in the leukemia population as opposed to normal individual. However, such rare alleles are not prone to mutagenesis in vivo.

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CML 03

STUDY OF CHROMOSOMAL ANOMALIES AND CELL SURFACE MARKERS IN THE BLAST PHASE OF PH^1-POSITIVE CHRONIC MYELOID LEUKEMIA

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Chromosomal abnormalities of the bone marrow were studied in thirtyfour Ph-positive patients by means of C-banding in the blast crisis of chronic myeloid leukemia (Ph-positive CML-BC). We found nonrandom chromosomal aberrations. Most frequently an i (17q), +8, or a second Ph-chromosome were found with or without additional atypical changes in some cases.
In one case the Ph-chromosome originated from an atypical translocation t(12;22) without other changes being present. All other cases showed the standard translocation t(9;22). Changes in the acute phase included a t(2;6), t(5;19), t(6;11), t(7;18), t(14;17), loss of chromosome 9 14, 19 and y or 6q-, 11q-, 9q-, 20q-.
In addition we investigated the surface antigen pattern of most patients. In two cases with atypical chromosomal changes the blast cells reacted strongly positive with C-ALL antibody against B-lymphocyts (B1, B4, Ia). Most cases of myeloid and myelomonocytic blast cells were characterized by chromosomal changes like +8, i (17q) or a second Ph-chromosome. In all cases studied we observed a decrease of the Vim D-5 marker, typical for mature granulocytic cells. The correlation between chromosomal anomalies, blast cell differentiation and the clinical course in the Ph-positive CML-BC allows a subclassification.

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CML 04

HIGHER RISK OF GRAFT-VERSUS-HOST-DISEASE IN PATIENTS WITH CHRONIC GRANULOCYTIC LEUKEMIA AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION?

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Allogeneic and syngeneic bone marrow transplantation (BMT) following a supralethal radiochemotherapeutic conditioning regimen is presently the sole mode of treatment for chronic granulocytic leukemia (CGL), which ensures long-lasting hematologic and cytogenetic remissions, hence offering the possibility of cure. Morbidity and mortality after allogeneic BMT using marrow of a related histocompatible donor is decisively influenced by the development of graft-versus-host-disease (GVHD). GVHD in turn appears to be dependent on the presence of human lymphocyte system A (HLA)- and non-HLA determinants, which are not qualitatively detectable utilizing routine serologic and cellular methods for immunogenetic donor selection.
At our center the overall incidence of GVHD in patients at risk (i.e. allogeneic transplantation, survival > 14 days post BMT) is 37% (40/108). Retrospective analysis of GVHD frequency in relation to the underlying disease revealed a markedly higher risk of developing GVHD in patients suffering from CGL (total n=35, chronic phase n=27, accelerated phase n=5, 2nd chronic phase n=3) as compared to patients having acute leukemia (AL) (n=59) or severe aplastic anemia (SAA) (n=14).
The total incidence is 63% (22/35) in CGL as opposed to 24% (14/59) in AL and 28% (4/14) in SAA. Concerning the clinical grading of acute GVHD, the acute severe forms (grade III-IV) predominate in CGL patients totaling 26% (9/35) as compared to 7% (4/59) in AL patients and 14% (2/14) in SAA patients. Since age distribution and prophylaxis of GVHD were uniform in all three disease groups, the question concerning the cause of the high GVHD incidence in patients having CGL remains unanswered.

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