According to the classification of neutropenia, 26 patients suffered from severe, 16 moderate, and 14 from mild neutropenia. Single episodes of transient neutropenia have been seen in 19 patients. Twenty-six had experienced chronic neutropenia and 11 cases had recurrent neutropenia (Table 2). Also, 32 out of these patients showed leukopenia (57.1%), 24 had anemia (42.9%), 11 thrombocytopenia, and only 3 patients had monocytosis. The most common infections during the course of the illness were respiratory infections, which were seen in 48 patients (85.7%). Other manifestations were: pneumonia (30 cases), otitis media (28 cases), acute diarrhea (28 cases), abscess (24 cases), oral candidiasis (23 cases), oral ulcers (17 cases), cutaneous infections (16 cases), and sinusitis (12 cases). Other less frequent infections were: periodontitis or conjunctivitis (5 cases), cystitis (2 cases), meningitis (2 cases), and osteomyelitis (1 case). Abscesses were detected in different sites, including: perianal (8 cases), cutaneous (7 cases), submandibular (4 cases), mastoid (3 cases), dental (3 cases), liver (2 cases), peritonsillar (2 cases), lung (1 case), and soft tissue (1 case). The non-specific signs of hepatomegaly and splenomegaly had already been found in 41.1% and 32.1% of the patients, respectively. All of the patients with single episodes of neutropenia had had infectious complications during the neutropenic episode, including: pneumonia (5 cases), otitis media (4 cases), diarrhea (2 cases), oral ulcers (2 cases), cutaneous infections (2 cases), abscess (2 cases), sinusitis (1 case), and oral candidiasis (1 case).

Neutropenia may occur in any PID as a consequence of either an intercurrent infection or an autoimmune disease. All of our patients with Shwachman-Diamond syndrome, cyclic neutropenia and Kostmann disease had associated neutropenia. In addition, a number of our patients with predominant antibody deficiency disorders had associated neutropenia. It seems that autoimmune neutropenia is a common cause of neutropenia in some primary specific immunodeficiencies. An increased susceptibility to infections was detected in our patients. For patients presenting with unexpected neutropenia, the clinical history and examination of the peripheral blood smear were the most important parts of the diagnostic evaluation. Examination of the oral cavity, perianal region, and skin is necessary in order to assess the clinical impact of chronic neutropenia. The presence of gingivitis, ulcer, and abscess implies clinically significant neutropenia. Persistent infections should always raise a suspicion which deserves further evaluation, of an underlying immune deficiency syndrome and neutropenia, because a delay in diagnosis may result in a serious organ damage or even death of the patient.

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Key words: neutropenia, immunologic deficiency syndromes, infection, Iran.

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References


Chronic Myeloid Leukemia

Chronic myeloid gene abnormalities in patients with chronic myeloid leukemia in complete cytogenetic response to imatinib mesylate

The emergence of chronic chromosomal abnormalities in Philadelphia-negative cells during treatment with imatinib in patients with Philadelphia-positive chronic myeloid leukemia has been reported. We add information to this issue presenting a series of 29 patients in complete cytogenetic response after imatinib treatment, three of whom developed clonal aberrations.

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Chronic myeloid leukemia (CML) is a chronic myelo-proliferative disorder (CMLD) characterized by the t(9;22)(q34.1;q11.2) that juxtaposes the ABL and BCR genes with generation of the Philadelphia chromosome (Ph1). The molecular consequence is the BCR-ABL oncoprotein, which encodes a BCR-ABL oncoprotein (p210BCRABL) with increased tyrosine kinase activity which is necessary and sufficient for leukemogenesis.1 Imatinib mesylate (STI571, Glivec®, Novartis Pharma, Switzerland), a tyrosine kinase inhibitor selective for ABL, BCR-ABL, c-KIT, PDGFRαs and ARG proteins has demonstrated good results in CML. As first line therapy, imatinib is superior to interferon (IFN)-α, inducing complete hematologic responses in 95% of patients, major cytogenetic responses in 85% and complete cytogenetic responses (CCR) in 73%.2 Imatinib has been proven to be better tolerated, although long-term side effects and influence on long-term survival are not yet known. Recently, some cases of chronic myeloid gene abnormalities in Ph- negative cells of patients with CML treated with imatinib have been
We describe the presence of clonal abnormalities in Ph' negative cells in patients diagnosed with CML treated with imatinib showing clonal cytogenetic abnormalities in Ph' negative cells.

<table>
<thead>
<tr>
<th>Case</th>
<th>Conventional cytogenetics</th>
<th>FISH (% abnormal cells)</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46,XX(20)</td>
<td>-7 (18%)</td>
<td>No dysplastic features</td>
</tr>
<tr>
<td>2</td>
<td>45,XY, -7[10] /46,XY[10]</td>
<td>-7 (44%)</td>
<td>Multilineage dysplasia not present at diagnosis</td>
</tr>
<tr>
<td>3</td>
<td>48,XY, +8[3] /46,XY[17]</td>
<td>+8 (36%), XXY (24%)</td>
<td>Megakaryocytic dysplasia not present at diagnosis</td>
</tr>
</tbody>
</table>

*Two hundred nuclei were analyzed for each different probe and patient.*
Submicroscopic deletions adjacent to the breakpoints of balanced translocations were identified in 9%-16% of all cases of chronic myeloid leukemia (CML) by interphase fluorescence in situ hybridization (FISH). The rate of hematologic and cytogenetic responses to imatinib was statistically significantly lower in patients with deletions.

So far only a few studies, with limited numbers of cases, have examined the incidence and prognostic impact of submicroscopic deletions in balanced translocations in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) (Table 1). We, therefore, determined the incidence of submicroscopic deletions in the most common balanced rearrangements in leukemia using interphase FISH. This study was based on 245 cases with CML, 79 patients with ALL, and 412 patients with AML, who were referred to our laboratory from January 2000 to April 2004. The cohort of patients with AML comprised 112 patients with AML-1-ETO, 108 patients with PML-RARα, 122 patients with CBFB-MYH11, and 96 patients with different MLL rearrangements. The cohort with ALL comprised 70 patients with BCR-ABL positive ALL and 29 patients with different MLL rearrangements. Cytogenetic analysis was performed in all cases. FISH was performed on interphase nuclei and/or metaphases on bone marrow smears or blood smears. We used a BCR-ABL two color/two fusion probe (Cancer Genetics, CGPT 07), a LSI AML1-ETO dual color, dual fusion translocation probe, a LSI PML-RARα dual color, dual fusion translocation probe, a LSI CBFB dual color, break apart rearrangement probe (Core Binding Factor β-subunit), and a LSI MLL dual color, break apart rearrangement probe (Abbot, 5J 63-01). At least 100 interphase nuclei were viewed for each case. The analyzing system, ISIS® (MetaSystems, Altusheim, Germany), was used for documentation.

In all cases the leukemia-specific fusion transcripts were also amplified by reverse transcription polymerase chain reaction (RT-PCR). For analysis of MLL fusions with partner genes in AML and ALL the respective RT-PCR was performed. In CML we found submicroscopic deletions in 9% of cases (22/245) with interphase FISH. In BCR-ABL positive ALL the incidence was 6% (4/70) and in ALL with MLL rearrangements it was 3% (1/29).

Submicroscopic deletions occur in 9-16% of patients with CML and are clearly associated with an inferior prognosis. We determined the incidence of submicroscopic deletions in the most frequent reciprocal translocations in acute leukemias, as well as in CML. Our results in CML (deletions in 9%) and in BCR-ABL positive ALL (deletions in 6%) were in the ranges reported in the literature. The incidence that was found in ALL with different MLL rearrangements was 3%, which is lower than published so far. We observed deletions in 3% of AML with PML-RARα and in 4% of AML with AML1-ETO. Kolomietz et al. did not find deletions in subtypes of AML; to our knowledge their study is the only other examination of submicroscopic deletions in these subtypes. The incidence of submicroscopic deletions in AML with CBFB-MYH11 was 2% in our study.

These data provide a strong indication that the frequency of these deletions is much lower than previously published (10-33%). We found submicroscopic del-