caused by virtually any drug, due to immunological and/or a local inflammatory reaction. Two patients had cutaneous erythema, associated in one case with transient pancytopenia and in the other with transient liver failure that rapidly resolved (10 days) after drug withdrawal. No other drug was involved in either case. Four females older than 60 years old (2 over 80) on HU (total dose 0.9–2.4 kg) for at least 3 years suffered from painful leg ulcers. None of them had diabetes. Three of them recovered within 1 month after drug withdrawal and were already being followed at our clinics. The other patient, who had undergone left leg Fogarty’s embolectomy 3 years previously, was referred to us after having continued treatment elsewhere for 3 months following appearance of the ulcer. Two further weeks later she underwent leg amputation because of intractable local infection and pain and finally died of myocardial infarction. Painful malleolar ulcers appear despite the lack of trauma or provoking agents other than HU. Most cases, as ours, had received about 1 g/day of HU per day for at least 1 year. These ulcers seem to result from cumulative toxicity of HU on the basal layer of the epidermidis due to inhibition of DNA synthesis. Treatment is difficult but must include prompt cessation of HU therapy. It has been suggested that HU treatment in myeloproliferative disorders increases the risk of acute leukemia. Besides some series reporting a nearly 10% risk by the 13th year of treatment, others stressed that leukemic transformation occurs in patients treated with other cytotoxic drugs. Our 3 patients who developed acute leukemia had received busulfan (BU) in the first period of their disease for 9 and 15 months, followed by a median of 7.5 years of HU treatment. The patient who developed pancreatic cancer had received BU and HU. However, a relation between HU and such a cancer seems improbable. We conclude that HU is a safe and useful drug in the treatment of myeloproliferative disorders. Prompt recognition of side effects, which are mostly minor and rapidly subside once the drug is withdrawn, is crucial in order to avoid more severe complications.

### References


### Acute Myeloid Leukemia

**Trisomy 11 in myeloid malignancies is associated with internal tandem duplication of both MLL and FLT3 genes**

In 20 patients with myeloid malignancies and isolated trisomy 11 an internal tandem duplication of the MLL and FLT3 genes was observed in 41% and 31% of the cases, respectively; 80% of the FLT3+ cases showed MLL self-fusion. Concomitant presence of MLL and FLT3 anomalies could be relevant in determining the poor outcome of patients with acute myeloid leukemia with trisomy 11.

**Isolated trisomy 11 is a rare aberration observed in myelodysplastic syndromes (MDS) and acute myeloblastic leukemia (AML). Molecular characterization of cases of AML with trisomy 11 has revealed a non-random association with a partial tandem duplication (PTD) of the MLL gene, leading to in-frame fusion of a portion of the proto-oncogene with itself. The incidence of this molecular anomaly in trisomy 11 cases of AML ranged from 20% to 73%. Internal tandem duplication (ITD) has been demonstrated as a oncogene-activating mechanism also in another gene involved in AML, namely the FLT3 gene, which encodes for a receptor tyrosine kinase widely expressed in hematopoietic cells and precursors.**

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**Table 1. Side effects of hydroxyurea (HU) in our patients with polycythemia vera (PV) and essential thrombocythemia (ET).**

<table>
<thead>
<tr>
<th>N° of cases</th>
<th>Sex F/M</th>
<th>PV/ET</th>
<th>HU mean dose (mg/day)</th>
<th>Median treatment duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>129</td>
<td>76/53</td>
<td>54/75</td>
<td>620±270</td>
</tr>
<tr>
<td>Drug failure</td>
<td>9</td>
<td>5/4</td>
<td>3/6</td>
<td>1,550±560</td>
</tr>
<tr>
<td>Complete response</td>
<td>120</td>
<td>71/49</td>
<td>51/69</td>
<td>600±245</td>
</tr>
<tr>
<td>Thrombotic complication</td>
<td>15</td>
<td>6/9</td>
<td>9/62</td>
<td>890±280</td>
</tr>
<tr>
<td>Early major side effects</td>
<td>4</td>
<td>1/3</td>
<td>1/3</td>
<td>1000±500</td>
</tr>
<tr>
<td>Late major side effects</td>
<td>10</td>
<td>7/3</td>
<td>3/7</td>
<td>750±250</td>
</tr>
<tr>
<td>Minor side effects (black nail pigmentation and macrocytosis without anemia)</td>
<td>54</td>
<td>36/18</td>
<td>19/37</td>
<td>620±270</td>
</tr>
</tbody>
</table>
FLT3/ITD occurs in approximately 20% of unselected adult patients with de novo AML and in 30–40% of AML with a normal karyotype. Co-duplication of MLL and FLT3 was observed in 2 cases of AML. It has been reported that FLT3/ITD is more common in patients with MLL/PTD (33%) than in cases with MLL translocations (8%). In a large series of adult AML analyzed for both molecular anomalies, the rate of MLL/PTD was significantly higher in FLT3 positive (8.7%) than in FLT3 negative (4.1%) patients, although this finding did not correlate with trisomy 11.

In 20 patients with myeloid malignancies carrying a trisomy 11 as a primary anomaly we analyzed clinical, immunological and cytogenetic data and correlated them with the presence of MLL/PTD and FLT3/ITD (Table 1). Bone marrow cells at diagnosis were studied for +11 by fluorescent in situ hybridization (FISH) with a centromeric probe for chromosome 11. The MLL gene was investigated with a combination of two PAC clones that cover the MLL gene with a minimal overlap in the breakpoint cluster region. Control experiments were performed on 10 normal bone marrow samples. The normal range was set as the mean +3SD. Southern blotting for the MLL gene and reverse transcription polymerase chain reaction (RT-PCR) identification of MLL and FLT3/ITD were done as reported elsewhere.

The diagnosis was AML, either de novo or secondary, in 15 patients, MDS in 4 cases, and accelerated myeloproliferative disorder in one case. Immunophenotyping showed consistent positivity for stem/progenitor cell markers, including CD34, HLA-DR, CD33 and CD13. Interphase FISH analysis confirmed the trisomy in all cases, in a percentage of cells ranging from 17% to 82%. MLL/PTD was observed in 7/17 (41.2%) cases, 6 with isolated trisomy 11 and one with additional anomalies. FLT3/ITD was analyzed in 16 patients and was found to be positive in 5 cases (31.2%). No case of MDS showed a structurally altered MLL or FLT3 gene, so the incidence of the two anomalies in AML patients was 54% and 38%, respectively. The overall incidence of FLT3/ITD was similar to that observed in patients with normal karyotype. However, 4 out of 5 (80%) of the FLT3/ITD positive cases also showed MLL/PTD, whereas only 3/11 (27.3%) of the FLT3/ITD-negative cases had MLL/PTD. Considering the MLL/PTD-positive cases, FLT3/ITD was found in 4/7 (57.1%), whereas only 1 of the 10 MLL/PTD-negative patients had FLT3/ITD. The median survival for the whole group of +11 cases was 14.5 months, 18 months for both the MLL and FLT3 negative groups and only 6 and 2 months for the patients who had a MLL or a FLT3 duplication, respectively (Figure 1).

Recently, co-duplication of MLL and FLT3 genes has been suggested as a possible marker of a common genotoxic stress; alternatively, it has been suggested that MLL rearrangements and FLT3 constitutive activation may cooperate in transformation. In our group of patients with trisomy 11, a close correlation was found between the two anomalies with a high percentage of co-duplication when compared to patients showing isolated duplication of MLL or FLT3.

The pathogenetic mechanism by which the MLL partial duplication leads to carcinogenesis is not clear. Recently, amplification of the MLL gene has been identified as a new consistent cytogenetic mechanism of MLL activation, mediated by the upregulation of a number of other genes. The gene expression profile in patients with MLL amplification is similar to that observed in MLL-rearranged acute leukemia. In patients with trisomy 11, the presence of a low-copy MLL amplification may have an etiologic role based on MLL gain of function.

FLT3/ITD appears to be quite common in patients with MLL self-fusion; it remains to be clarified whether the co-expression of the two anomalies may depend on a common pathogenetic mechanism or merely represent cooperation in multistep leukemogenesis, possibly being
Letters to the Editor

Acute Lymphoblastic Leukemia

γδ and γδ T-cell acute lymphoblastic leukemia: comparison of their clinical and immunophenotypic features

Acute lymphoblastic leukemia (ALL) is a rare variant of ALL. The comparison of some clinical and laboratory features in children and adults with γδ-T-ALL or γδ-ALL showed that in γδ-T-ALL the CD45RA+/CD45RO− phenotype was predominant, the hemoglobin concentration was lower in children and the presence of splenomegaly and the white cell counts was higher in adults.

Relevant in determining the poor outcome observed in patients with trisomy 11.

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Key words: trisomy 11, MLL partial tandem duplication, FLT3 internal tandem duplication.

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