Blood dyscrasias in clozapine-treated patients in Italy

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ABSTRACT

Background and Objectives. Clozapine is a dibenzoazepine derivative that is more effective than standard neuroleptic drugs in refractory schizophrenic patients, but its introduction in some countries was delayed by its propensity to cause blood dyscrasias. However, over the last ten years, different reports have clearly demonstrated that agranulocytosis and neutropenia can be easily prevented by means of strict hematologic surveillance. This article reviews the results of the first five years of the Italian Clozapine Monitoring System (ICLOS).

Design and Methods. The hematologic parameters of 2,404 patients registered between 1995 and 1999 were collected in a central database, before the patients began clozapine-treatment, weekly for the first 18 weeks, and then monthly throughout the duration of therapy. On the basis of conventional criteria, different risk levels have been identified with total leukocyte <3.0×10^9/L and/or an absolute neutrophil count <1.5×10^9/L leading to immediate discontinuation of the drug.

Results. The analysis shows that 0.9% of the patients developed neutropenia and 0.7% agranulocytosis, mainly during the first 18 weeks of clozapine treatment. Drug discontinuation led to the normalization of hematologic parameters in all cases, reversal of agranulocytosis, and to avoid drug re-exposure in schizophrenic patients who have previously had to discontinue treatment because of the occurrence of other blood alterations, particularly leukocytosis and eosinophilia.

Interpretation and Conclusions. The ICLOS study confirms that regular hematologic monitoring is highly effective in minimizing the incidence of clozapine-associated blood dyscrasias. Surveillance reports from different countries have shown that the risk of agranulocytosis and neutropenia is respectively 0.38% and 1.5-2.9% as a result of hematologic monitoring, these rates decrease significantly after the first year of treatment, as does the risk of death due to secondary complications.

The aim of this paper is to describe the results of the Italian Clozapine Monitoring System (ICLOS) in relation to the risk of agranulocytosis and neutropenia in 2,404 clozapine-treated patients registered between 1995 and 1999, and to discuss related aspects such as the role of predisposing risk factors and the occurrence of other blood alterations, particularly leukocytosis and eosinophilia.

Design and Methods

Clozapine (Leponex – Novartis) came onto the Italian market in 1995, when the ICLOS monitoring service was independently set up by the Institute of Advanced Biomedical Technologies of the Italian National Research Council (CNR). The main purpose of this service is to support psychiatrists in the management of cases of clozapine-induced neutropenia and agranulocytosis, and to avoid drug re-exposure in schizophrenic patients who have previously had to discontinue treatment because of the occurrence of such hematologic side-effects. This is done by collecting demographic, case history and hematologic data. The hematologic parameters are evaluated before...
the beginning of treatment, weekly for the first 18 weeks, and then monthly throughout the duration of therapy. The data are promptly sent to the CNR by the physician responsible for the psychiatric center via modem, on a floppy disk or on paper (in the case of any delays in sending blood parameters, the physician is contacted by telephone), and are subsequently entered in a central database in which the patients are identified by means of a code that respects their anonymity.

The hematologic toxicity of clozapine is determined on the basis of criteria indicated in the international literature, which define leukopenia as a total leukocyte (WBC) count of less than 3.5×10^9/L, neutropenia as an absolute neutrophil count (ANC) of 1.5-0.5×10^9/L, and agranulocytosis as a reduction in the neutrophil count to less than 0.5×10^9/L. The monitoring is therefore structured in such a way as to identify three risk levels: 1) a yellow alarm when the WBC count is <3.0×10^9/L and/or the ANC is 1.5-2.0×10^9/L, which requires a hematologic evaluation to be made every three days; 2) a pink alarm when the WBC count is <3.0×10^9/L and/or the ANC is 1.0-1.5×10^9/L, which implies the immediate discontinuation of the drug; and 3) a red alarm when the ANC is <1.0×10^9/L.

In addition to leukocyte counts, the monitoring includes collection of data relating to other hematologic parameters such as absolute eosinophil (AEC) and platelet (Plt) counts, as well as data concerning any non-hematologic effects attributable to clozapine and the psychopathologic status of the patient. As of March 1999, the monitoring system involved 542 psychiatric centers which had transmitted data relating to 2,404 schizophrenic patients: 30% of the centers used a modem, the others used floppy disks or paper. Table 1 summarizes the clinical characteristics of the ICLOS-registered patients. The majority of patients who had agranulocytosis (0.7%). In four patients (two with neutropenia and two with agranulocytosis), clozapine was administered together with other potentially myelotoxic drugs (carbamazepine, lamotrigine, methimazole).

As far as hematologic dyscrasias are concerned, 40 patients (19 males and 21 females with a mean age of 40.7±3.4 years, representing 1.7% of the treated population) discontinued clozapine because of the appearance of neutropenia or agranulocytosis within the first 18 weeks of beginning the therapy (89% of the cases) or between 18 and 78 weeks after initiating treatment (11%). Two of these patients were withdrawn from the analysis: one because the appearance of undifferentiated blastic cells in bone marrow and peripheral blood during neutrophil recovery led to a diagnosis of acute myeloid leukemia; the other because the peripheral differential count revealed a non-neutropenic leukopenia.

As shown in Table 2, ICLOS also identifies hematologic alterations other than neutropenia and agranulocytosis. Neutrophil leukocytosis (WBC count of...
Mild eosinophilia (AEC >0.4×10^9/L) was more frequent in males (117 cases = 9%) than females (55 cases = 6.4%). Mild eosinophilia (AEC >0.4×10^9/L), unrelated to concomitant pathologies and with no difference between the sexes, was observed in 52 patients (2.2%) after a median drug exposure of 27 days. None of the leukocytosis or eosinophilia cases required the interruption of clozapine administration, and all spontaneously resolved 3-4 weeks after onset. Finally, only two patients experienced mild thrombocytopenia (Plt count of 80×10^9/L), which rapidly normalized after drug discontinuation.

**Discussion**

The use of psychotropic drugs has long been considered one of the major causes of blood dyscrasias. A critical evaluation of the literature reveals that the incidence of agranulocytosis and mild transient neutropenia among phenothiazine users is about 0.08% and 8.9% respectively. Furthermore, the propensity of antipsychotic drugs to affect myeloid series was dramatically illustrated by an early Finnish study during which the mortality rate was 50% among the 16 patients who developed agranulocytosis after clozapine treatment. After a long period of severely restricted use, compassionate clozapine trials started again in the mid-1980s as a result of pressure from psychiatrists who had no other compounds that were effective in cases of resistant schizophrenia. These studies confirmed the risk of agranulocytosis but also underlined the beneficial effect of hematologic monitoring, which became mandatory when clozapine once again became easily available on the market. In Italy, blood cell counts are made weekly for the first 4-5 months, and then monthly until the end of therapy. The results from the databases of the national registries of patients monitored in the USA, UK, Ireland, France, Canada and Australia showed that the incidence of clozapine-induced agranulocytosis is about 0.8%, which is in line with the more recent ICLOS data reported in the present paper. However, the 0.9% incidence of clozapine-related neutropenia in Italy is much lower than the 2.9% reported in American and British patients; this difference is probably due to the fact that for Italian psychiatrists adhesion to the ICLOS study is optional. Furthermore, an important finding emerging from ICLOS and other epidemiologic studies is that the risk of developing neutropenia and agranulocytosis clearly exists during the first 18 weeks of therapy, but decreases significantly after the first year and is similar to that observed with some phenothiazines whose use is not associated with regular blood testing. The favorable impact of early detection of dyscrasias in susceptible patients has been recently highlighted by a post-marketing surveillance analysis of 99,502 American patients over a five-year period. This study clearly shows that the rate of agranulocytosis has significantly decreased to 0.38%, and the risk of death to 0.012% instead of the higher value initially observed in Finland. The early administration of subcutaneous G-CSF or GM-CSF has further reduced the morbidity and mortality of clozapine-induced agranulocytosis on the basis of various other reports as well as the ICLOS data, the use of growth factors can be considered warranted in high-risk patients who gradually reach the absolute neutrophil threshold level or those who have rapidly declining leucocyte counts. Further advantages are cost-savings due to the possibility of avoiding hospitalization and the use of broad spectrum antibiotics and antifungal agents for febrile neutropenia. The ICLOS analysis does not reveal any significant predisposing factors but, in agreement with occasional reports in the literature, suggests that the concomitant administration of other potentially myelosuppressive drugs may increase the risk of neutropenia and agranulocytosis.

**Table 2. Hematologic side effects in 2,404 ICLOS-registered patients treated with clozapine.**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>No. of patients</th>
<th>Incidence (%)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Neutropenia (ANC 0.5-1.5×10^9/L)</td>
<td>22</td>
<td>0.9%</td>
<td>complete recovery in all patients</td>
</tr>
<tr>
<td>Agranulocytosis (ANC &lt; 0.5×10^9/L)</td>
<td>16</td>
<td>0.7%</td>
<td>complete recovery in all patients</td>
</tr>
<tr>
<td>Leukocytosis (WBC 15.0-21.0×10^9/L)</td>
<td>185</td>
<td>7.7%</td>
<td>spontaneous resolution in all patients</td>
</tr>
<tr>
<td>Eosinophilia (AEC &gt; 0.4×10^9/L)</td>
<td>52</td>
<td>2.2%</td>
<td>spontaneous resolution in all patients</td>
</tr>
<tr>
<td>Thrombocytopenia (Plt &lt; 100×10^9/L)</td>
<td>2</td>
<td>-</td>
<td>spontaneous resolution in both cases</td>
</tr>
</tbody>
</table>
Other transient hematologic abnormalities have been described during clozapine treatment. Mild anemia or thrombocytopenia sometimes occurs but does not usually require the discontinuation of therapy; in such cases, the possibility of pre-existing underlying diseases or external factors causing pseudo-thrombocytopenia should be carefully investigated. Furthermore, a small number of patients develop leukocytosis as a result of TNF-alpha stimulation which increases endogenous G-CSF production. More interesting is the finding of early and transient leukocytosis, which may predict an increased risk of agranulocytosis; however, it has recently been demonstrated that this also occurs in patients whose neutrophil counts do not fall. Similarly, transient and asymptomatic eosinophilia, which has been encountered in 0.2%-6.7% of clozapine-treated patients, may be an immunologic signal predicting incipient neutropenia or agranulocytosis. The ICLOS study does not support this hypothesis but suggests other physiopathologic explanations that take into account the role of the compensatory cytokines released by clozapine treatment.

How clozapine affects hematopoiesis is still unknown, but the existence of a peripheral immunomediated mechanism is supported by the fact that the cytotoxic activity observed in the serum of patients with agranulocytosis is attenuated by antibodies to IgM immunoglobulin. The association with some HLA haplotypes suggests a genetic background that may induce the production of autoantibodies, as in the case of patients with idiopathic hydralazine-induced systemic lupus erythematosus. However, a direct toxic effect on hematopoiesis is more likely because patients with clozapine-induced agranulocytosis generally show a slow decline in neutrophil levels and do not have any myeloid precursors in bone marrow.

One neutropenic patient was excluded from the ICLOS analysis because acute myeloid leukemia developed after treatment with G-CSF. This case deserves particular mention because clozapine clearly interferes with the maturation and differentiation processes of hematopoiesis in vitro, and isolated cases of various types of leukemia have been reported in the literature. However, a number of factors make it possible to exclude the hypothesis that clozapine is leukemogenic: the reported rate of occurrence lies within the background incidence of leukemia in the general population, no dysplastic morphologic changes have been documented in the bone marrow or peripheral blood of patients with agranulocytosis, and no neoplastic growth pattern has been observed in cells cultured in vitro in the presence of clozapine or its metabolites.

In conclusion, the international and ICLOS registries clearly show that regular blood count monitoring is a highly effective means of minimizing the incidence of clozapine-associated blood dyscrasias. Furthermore, the availability of growth factors contributes towards reducing the risk of fatal agranulocytosis complications to a minimum. These results are encouraging when it is borne in mind that, as in the USA population, about 30% of Italian schizophrenic patients do not respond adequately to standard antipsychotic agents and are thus potential candidates for clozapine treatment. Furthermore, it has recently been reported that clozapine might offer substantial therapeutic benefits in other neurologic disorders such as Parkinson’s disease.

Potential implications for clinical practice
- The risk of clozapine-associated neutropenia and agranulocytosis is lower than initially expected.
- Regular monitoring and early administration of growth factors significantly reduce the risk of fatal clozapine-induced agranulocytosis.

References