Brief Communication

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Granulocyte Colony-Stimulating Factor for Neutropenia Secondary to Ticlopidine

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Neutropenia is an uncommon, albeit serious, toxic effect of several non-antineoplastic drugs, like ticlopidine. Nowadays, recombinant growth factors are available as therapeutic agents, but they are not currently used for toxic neutropenias. We report three cases of severe neutropenia due to ticlopidine, with an excellent outcome after early treatment with granulocyte colony-stimulating factor (G-CSF).

The first patient was a 65-year-old male, who suffered a stroke in May 1991. Treatment was started with acenocumol, which was replaced by ticlopidine in February 93. As severe diarrhoea developed a month later, triflusal was substituted for ticlopidine in March 93. During the following days, diarrhoea continued and the patient became febrile, so he was admitted to the hospital. He had an axillary temperature of 38 °C, but no other signs were found on physical examination. The WBC was $3.2 \times 10^9/l$ with an absolute neutrophil count (ANC) of $0.12 \times 10^9/l$. Bone marrow examination showed a decrease in the myeloid precursors to 44% and granulopoietic maturation arrest; the erythroid and megakaryocytic series remained unchanged. Blood cultures were sterile. Ticlopidine was stopped and the patient was started on broad-spectrum antibiotics and G-CSF, 48 MU (480 µg) subcutaneously q.d. After one dose, he became afebrile and the ANC rose to $5.1 \times 10^9/l$; an extra dose was given. He was discharged 3 days later, when diarrhoea subsided, with an ANC of $10 \times 10^9/l$.

The second patient was a 78-year-old male with arterial hypertension and mild chronic renal failure. He suffered a brain infarction in 1988 and Wallenberg's syndrome in December 92. He had been on enalapril and nifedipine treatment for years, and started ticlopidine after the last cerebrovascular event. He was admitted in March 93 because of a 5-day history of fever. His axillary temperature was 39 °C. The WBC was $1.0 \times 10^7/l$ with an ANC of $0.24 \times 10^7/l$. Bone marrow aspirate showed rich cellularity, but the myeloid precursors were almost absent. Erythroid and megakaryocytic series were not diminished. Blood cultures were negative. All drugs were stopped, and therapy was started with broad-spectrum antibiotics and G-CSF, 48 MU (480 µg) subcutaneously q.d. After one dose, he became afebrile. After 10 doses the ANC was $2.5 \times 10^7/l$. He was discharged 11 days after admission.

The third patient was a 40-year-old male, previously diagnosed as suffering from severe psoriatic arthritis, arterial hypertension and pulmonary thromboembolism. He had been taking enalapril for 1 year and ticlopidine for 2 months. He was admitted to the hospital in November 92 because of a 6-day history of fever. On admission, physical examination was normal; axillary temperature was 38.5 °C. The WBC was $0.3 \times 10^9/l$ and the ANC was 0. Bone marrow examination was not available. Ticlopidine was stopped and he was started on G-CSF 48 MU (480 µg) subcutaneously q.d. and broad-spectrum antibiotics. After one dose, he became afebrile. After 3 doses, the ANC was $3.4 \times 10^7/l$; an extra dose was given. He was discharged on day 8. The WBC was $11.4 \times 10^9/l$, and the ANC $9.5 \times 10^7/l$.

Severe neutropenia is a potentially lethal toxic effect of several non-antineoplastic drugs. Ticlopidine causes this side effect in roughly 1% of treated patients [1], usually within the first 3 months of treatment. It is due both to immunologically mediated and direct toxicity [2]. Spontaneous resolution usually occurs within a variable period of time, which is closely related to the state of myeloid series in the bone marrow: if it is rich in myeloid precursors, recovery begins within the first week after stopping the offending drug; but if marrow is depleted of such precursors, it may last for almost 2 months [3]. The final outcome is also influenced by other factors, like advanced age, low leukocyte and lymphocyte counts, high number of plasma cells in the marrow, renal failure, bacteraemia and shock [4].

G-CSF is a cytokine available for clinical use. It has a selective effect on the granulocytic precursors resulting in an apparent rise of circulating neutrophils [5-7]. Although, there is not much experience with G-CSF as a treatment for toxic neutropenias [8-10], the reported results, all of them anecdotal, are promising.

Our three patients showed different combinations of severity criteria on admission [3,4]: low WBCs, age over 60 years and diminished myeloid precursors in the two exam-

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ined bone marrows. After early treatment with G-CSF in the recommended dosage, two of them reached neutrophil levels greater than $2.0 \times 10^9/l$ within 1 and 3 days, respectively; it took 10 days to the 3rd patient. Moreover, all three became afebrile within 24 h after initiation of G-CSF treatment, although the ANCs were not substantially increased in two of them at that time. This might support a stimulatory effect on the mature circulating neutrophils, as has been pointed out by other authors [6,7]. No patient suffered any adverse reaction.

In summary, we believe that G-CSF and other related drugs might eventually play an important role in the management of severe toxic neutropenias, since they are very active molecules with few side effects. However, their actual efficacy should be defined in controlled clinical trials, which might be rather difficult as the cases are so few.

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