Prognostic factors of hematologic recovery in non-chemotherapy drug-induced agranulocytosis

We studied several factors that may influence the duration of hematologic recovery to reach neutrophil counts (>0.5 and 1.5×10⁹/L) and thus, indirectly, the prognosis in 91 patients with well-established drug-induced agranulocytosis. Multivariable analysis showed that neutrophil count <0.1×10⁹/L and infection profile (severe infections or septic shock) adversely influenced the neutrophil recovery (for the 2 neutrophil levels). Hematopoietic growth factors were significantly associated with rapid hematologic recovery (for the 2 neutrophil levels). Documented infection and antiplatelet agent-induced agranulocytosis were associated with rapid hematologic recovery (for a neutrophil count >1.5 ×10⁹/L).

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Non-chemotherapy drug-induced agranulocytosis (DIA) is a life-threatening disorder with a mortality of 5 to 15%.[1-3] To date, little information is available about the factors that may influence the duration of hematologic recovery and thus indirectly the prognosis.[1,4] From January 1985 to January 2000, we registered all cases of DIA among hospitalized patients (n=91). Data from this cohort (particularly inclusion criteria) have been published elsewhere.[5]

Using univariate and multivariate analyses with Cox's proportional hazard models, we determined the prognostic factors for hematologic recovery, defined as neutrophil counts >0.5 and >1.5×10⁹/L. Data were analyzed with the χ^2 test, the Mann-Whitney test and the t-test for paired data. Statistical significance was set at $p<0.05$.

Details of the clinical characteristics of the patients have been published elsewhere.[5,6] The median age of the patients was 64.5 years (range: 17 to 95); about two thirds were female. One third had chronic underlying diseases (diabetes, renal or heart failure, rheumatoid arthrits, etc.). The main clinical features during hospitalization included isolated fever (41%) and bacteremia or septic shock (34%). The remaining patients had severe infections, particularly pneumonia (10%). A pathogen was isolated from blood cultures in 30% of the patients, The mean (± SD) neutrophil count at diagnosis was 0.13±0.18×10⁹/L (range: 0 to 0.46). Sixty-five percent of patients had a neutrophil count <0.1×10⁹/L.

The most common causative classes of drugs were antibiotics (29%), antithyroid drugs (20%), antiplatelet agents (15%), non-steroidal anti-inflammatory agents (6.5%) and noramidopyrine (6.5%).

The outcome was favorable in 95.6% of subjects; 2 elderly patients died. The mean time to reach neutrophil count >0.5×10⁹/L and >1.5×10⁹/L was 8.9±4.6 days (range, 2-21) and 9.3±4.6 days (range: 2-21), respectively. Results of univariate and multivariate analyses are reported in Tables 1 and 2. By univariate analysis, hematopoietic growth factors (HGF), antiplatelet agents and isolated fever (versus bacteremia or septic shock and versus severe deep infections) were found to be significantly associated with better hematologic recovery (all $p<0.05$). The multivariate analysis revealed that variables associated with a poor neutrophil recovery were: neutrophil count <0.1×10⁹/L (versus 0.1-0.25×10⁹/L and versus ≥0.25 ×10⁹/L), bacteremia or septic shock and severe infections (versus isolated fever) (all $p<0.05$). On the other hand, the analyses showed that the HGF were associated with a significantly faster neutrophil recovery: mean reduction of 2 day) ($p<0.0001$). Furthermore, documented infection and an antiplatelet agent-induced agranulocytosis were variables associated with a more rapid hematologic recovery to a neutrophil count >1.5×10⁹/L (all $p<0.05$).

Table 1. Univariate analysis of variables influencing the time to neutrophil recovery >0.5 and >1.5×10⁹/L in 91 patients with non-chemotherapy drug-induced agranulocytosis.

	p value for neutrophil count >0.×10⁹/L	*p value for neutrophil count >1.5×10⁹/L*
Hematopoietic growth factor treatment	0.0001	0.0002
Antiplatelet agents	0.0179	0.0009
Infectious profile*	0.0500	0.0449
Antibiotics	0.0618	0.0514
Antithyroid drugs	0.0899	0.0609
Bone marrow profile	0.0995	0.0852
Number of neutrophils°	0.2939	0.2706
Chronic underlying disease	0.3128	0.4312
Age	0.3927	0.1061
Sex	0.8028	0.9991
Documented infection	0.9785	0.9794

**Isolated fever versus septicemia or septic shock versus severe infections (pneumonia, soft-tissue infections); °neutrophil count <0.1×10⁹/L versus 0.1-0.25×10⁹/L versus ≥0.25-0.5×10⁹/L.*

Table 2. Multivariate analysis of variables influencing the time to neutrophil recovery >0.5 and >1.5×10⁹/L in 91 patients with non-chemotherapy drug-induced agranulocytosis.

	p value for neutrophil count >0.5×10⁹/L	*p value for neutrophil count >1.5×10⁹/L*
Hematopoietic growth factor treatment	<0.0001	<0.0001
Neutrophil count <0.1×10⁹/L*	0.00090	0.00070
Isolated fever°	0.00220	0.00090
Antiplatelet agents	0.05530	0.02070
Documented infection	0.08390	0.04210

**Neutrophil count <0.1×10⁹/L versus 0.1-0.25×10⁹/L versus ≥0.25-0.5×10⁹/L. °Isolated fever versus septicemia or septic shock versus severe infections (pneumonia, soft-tissue infections).*

The outcome and prognosis of DIA are dependent on a variety of factors,[1,2] two of the most important factors being the severity (<0.1×10⁹/L) and the duration of the neutropenia.[1,4] Other factors such as age (>70 years), renal failure (creatinine level >20 mg/L), presence of bacteremia and shock, and bone marrow myeloid hypoplasia have also been associated with a

poor prognosis and survival.[4] We previously demonstrated that HGF may reduce the duration of the neutropenia and thus, indirectly, improve prognosis.[6]

The present data did not confirm the negative impact on hematologic recovery of age, renal failure or bone marrow appearance (Tables 1 and 2), but they confirm that: (i) neutrophil count $<0.1\times10^9$/L and the presence of bacteremia, septic shock or severe infections are associated with a poor neutrophil recovery; (ii) treatment with HGF is associated with a significantly faster neutrophil recovery (Table 2). These data are consistent with those reported in several other recent studies.[7,8] However, it should be noted that the only randomized trial in agranulocytosis induced by antithyroid drugs did not confirm the benefit of granulocyte colony-stimulating factor.[9] The present data demonstrated that a documented infection and diagnosis of antiplatelet agent-induced agranulocytosis were associated with a faster hematologic recovery (Table 2). One explanation might be that the patients treated with antiplatelet agents (e.g. ticlopidine) were closely monitored and that the drug was quickly withdrawn if neutrophil counts decreased.[10]

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Defective expression of the dihydrofolate reductase gene in patients with 5q- syndrome

We evaluated dihydrofolate-reductase (DHFR) gene expression in the marrow cells of 6 cases of 5q- syndrome and 8 patients with other myelodysplastic syndromes. DHFR mRNA was decreased in 5q- cases. Losses of transcripts were associated with low erythroblast DHFR activity, decreased progenitor growth *in vitro* and reduced erythroblast proliferative rate.

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The importance of the dihydrofolate reductase (DHFR) system is related to the key role of tetrahydrofolate in the transfer of the monocarbon unit and therefore in the synthesis of adenine and guanine bases. The human DHFR gene, 30kb long and constituted of 6 exons and 5 introns, has been mapped on the chromosome 5q11.2-q13.2.[1-3] Since abnormalities in the expression of DHFR may directly influence some phases of cell differentiation and proliferation and contribute to altering the homeostatic balance between cell growth and death, which is one of the most important physiopathologic mechanisms of myelodysplastic syndromes (MDS), we studied the expression of the DHFR gene in bone marrow cells of patients with the 5q- syndrome, to evaluate the possible role of the enzyme abnormality in the still obscure pathogenesis of the disease.[4-8]

We studied bone marrow aspirates from 6 patients with the 5q- syndrome, from 8 patients with other types of MDS, at the onset, not previously treated, and from 10 age-matched subjects without blood diseases. DHFR cytochemical reaction was performed on bone marrow smears.[9] For each erythroid cell in every specimen the optical density (OD) of the reaction product was determined by Vickers M86 scanning and integrating microdensitometry at $\lambda = 585\pm5$ nm. Total RNA was extracted by means of Trizol Reagent (Invitrogen) and evaluated and quantified by spectrophotometric analyses, using a biophotometer (Eppendorf). One microgram of total RNA for each sample was retro-transcribed using random hexamers and the High Capacity Archive kit (Applera), at 37°C for 2 hours. cDNAs were purified by Qiaquick spin columns (Qiagen). The structure and nucleotide sequence of the human DHFR gene were deduced based on the GenBank sequence AC022223. A Taq-