domain of the G-CSFR. Therefore, we suggest that patients with severe congenital neutropenia who acquire a point mutation in the cytoplasmic domain of the G-CSFR may represent the subgroup of patients in whom the neutropenia is a preleukemic disorder. However, the molecular mechanisms for the leukemogenesis between the point in time when G-CSFR mutations occur and overt leukemia remains to be investigated. Other genetic aberations such as loss of chromosome 7 (monosomy 7) or mutations in oncogenes, eg, ras-mutations,[10] might be subsequent steps in the development of leukemia.

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Paroxysmal Nocturnal Hemoglobinuria: Efficacy of Prolonged Treatment With Granulocyte Colony-Stimulating Factor

To the Editor:

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematopoietic disease characterized by abnormal red blood cells with complement-mediated hemolysis associated with a somatic mutation in a totipotent hematopoietic stem cell. Different cytopenias raise the question of the relation between aplastic anemia (AA) and PNH.[1] The biochemical defect underlying PNH is a deficiency in the biosynthesis of the glycosylphosphatidylinositol (GPI) anchor which is caused by a somatic mutation of the PIG-A gene localized to the X chromosome. In one case of PNH, we show the efficiency of long term granulocyte colony-stimulating factor (G-CSF) administration to correct severe neutropenia with granulocytes of the abnormal clone.

CASE REPORT

The diagnosis of PNH was established in October 1987 in a 16-year-old girl admitted for pancytopenia without splenomegalia: hemoglobin concentration was 66 g/L; mean corpuscular volume, 97 FL; reticulocyte count 130,000/μL; white blood cell (WBC) count, 2,000/μL, 29% of which were neutrophils; platelet count, 49,000/μL. Acid hemolysis test and sucrose lysis test were positive. Hemosiderinuria was detected. Bone marrow examination show no abnormal infiltration. Therapy with androgens was successful: reduced abdominal pain, episodes and anemia corrected (hemoglobin [Hb] level, 124 g/L); platelets were 243,000/μL whereas neutrophils remained below 1,000/μL. In May 1990, treatment was stopped because of virilism. From May 1990 to December 1992, minimal infectious problems resulted in hemolytic episodes and blood transfusions. At this date, while the neutrophil count decreased to less than 500/μL and a perianal abscess led to surgical treatment, the temperature was 40°C and antibiotic treatment was ineffective. On account of the severity of this infectious complication, G-CSF (Neupogen; Roche, Neuilly, France) was administred at a dose of 5 μg/kg subcutaneously once daily (275 μg). One week later, the neutrophil count was 7,000 and the patient had recovered. The growth factor treatment was then stopped. In July 1993, the neutrophil count was less than 100/μL and surgery was again necessary because of a perineal abscess. G-CSF treatment was restarted and 20 days later the neutrophil count was 2,500/μL. Karyotype control was normal. Bone marrow culture show a weak number of colony-forming unit-granulocyte macrophage (CFU-GM) colonies with a normal cluster/colony ratio. Since this date, the patient has benefitted from G-CSF treatment at a decreasing rate, which is now 60 μg per day (Fig 1). The result is dramatic: since July 1993, no blood transfusions have been required. From time to time, viral infections of the respiratory upper tracts with rhinorrhea, sneezing, and nasal congestion are observed. Rare hemolytic episodes are responsible for a moderate anemia without requiring transfusion. In January

1997, the hemoglobin level was 91 g/L, the neutrophil count was 2,750, and the platelet count 110,000. Flow cytometric studies have confirmed the absence of GPI-linked proteins: PNH affected cells represented about 50% of erythrocytes as determined using CD55 or CD59 monoclonal antibodies, 20% of lymphocytes (CD48), 95% of monocytes (CD14), and 98% of neutrophils (CD16 and CD66b). CD16 expression was observed at intermediate level whereas CD66b expression was abolished on all neutrophils. (Fig 2).

DISCUSSION

To our knowledge, the use of G-CSF treatment alone in typical cases of PNH over prolonged periods has not been examined. Webb and Bundtzen have reported the effect of GM-CSF on PNH.[2] A 69-year-old white woman thought to have a myelodysplastic syndrome was treated with GM-CSF and had an adverse reaction resembling capillary leak syndrome. Later, the diagnosis of PNH was established. Nimomiya et al[3] reported the effect of G-CSF in two patients during three clinical courses (2 μg/kg/d) with a transitory enhancement of the WBC polynuclear count. Schubert et al[4] treated a female PNH patient with severe thrombocytopenia, anemia, and granulopenia with G-CSF associated with cyclosporine. A trilineage response was observed with a significant increase of normal granulocytes and monocytes within 8 weeks.[4] Lastly, Jin et al[5] present evidence for the emergence of GPI-positive blood cells after treatment by antithymocyte globulin and G-CSF in a case of myelodysplasia associated with an AA PNH clone. At present, despite better understanding of the biochemical defect underlaying PNH, treatment remains supportive. Bone marrow transplantation remains a candidate therapy although the risks clearly limit its usefulness. In addition, the possibility of spontaneous remission and long-term survival argues against the use of bone marrow transplantation.[1] In our case, HLA studies suggested the possibility of a sibling allogenic bone marrow transplantation. For the moment, the patient refuses this option. Growth factor treatment therefore appears as an obvious alternative. However, it raises different questions concerning the risk of acute transformation or medullary depletion leading to AA. If one considers that the PNH clone is of malignant origin it is clear that G-CSF treatment poses the risk of proliferation of this clone. On the other hand, because there is no clear evidence to suggest that the PNH clone is malignant, G-CSF treatment could be considered without risk in this respect.

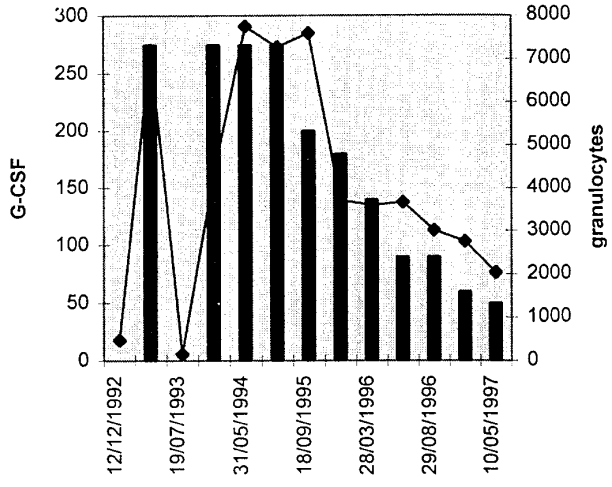

Fig 1. Variations in the number of granulocytes (microliters) in relation to G-CSF administered (micrograms per day). Dramatic increases in the number of granulocytes was observed when G-CSF was administered.

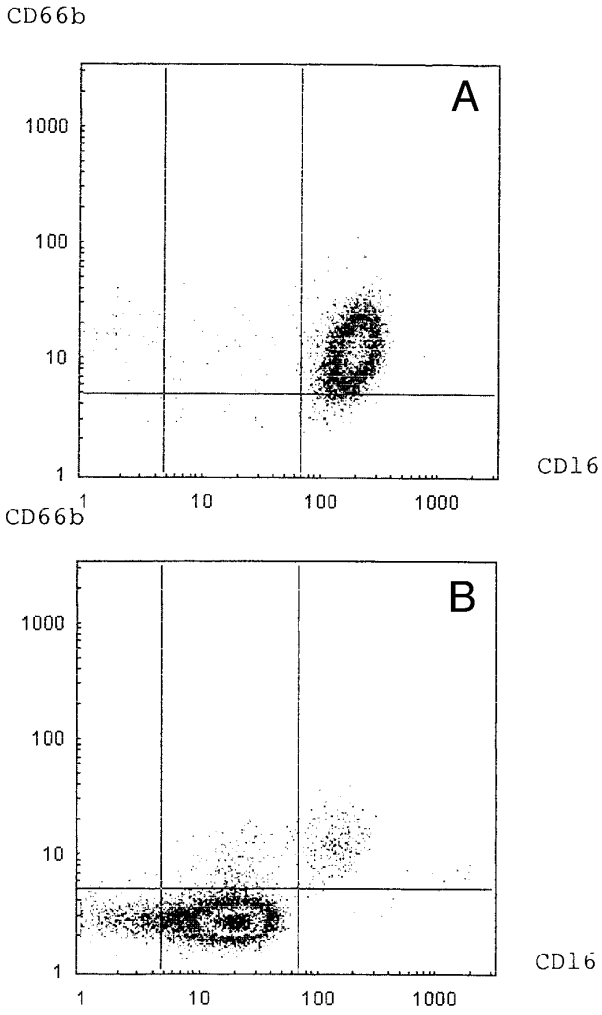

Fig 2. (A) Flow cytometry study of polymorphonuclear cells from a normal volunteer. Coexpression of GPI-linked proteins is detected with a CD16 monoclonal antibody (clone 3G8, P.cy5 labeled Immunotech France [Marseille], horizontal axis) and a CD66b monoclonal antibody (clone 80H3, FITC labeled Immunotech, vertical axis). (B) Flow cytometry study of polymorphonuclear cells from the patient treated with G-CSF. Normal coexpression of both CD16 and CD66b is observed in only 2% of the cells. The abnormal clone, which constitutes 98% of the population is characterized by a low expression of CD 16 without expression of CD66b.

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Application of the International Scoring System for Myelodysplasia to M.D. Anderson Patients

To the Editor:

In the March 15, 1997 issue of *Blood*, Greenberg et al[1] described a new International Prognostic Scoring System (IPSS) for evaluating prognosis in patients with myelodysplastic syndromes (MDS). To determine the effectiveness of the IPSS in patients not used to derive this system, we applied the IPSS to M.D. Anderson patients with MDS. The patients reported by Greenberg et al did not receive AML-type chemotherapy. Because after 1990 our practice was to give such therapy to patients with refractory anemia with blasts in transformation (RAEB-t) and to most patients with RAEB, we limited our analysis to patients seen before 1991. Like Greenberg et al, we included only patients with primary MDS, patients in whom a karyotype was obtained, and chronic myelomonocytic leukemia (CMML) patients only if they presented to us with a white blood cell count (WBC) below 12,000/μL. Such patients (n = 219) comprised 57% of the 381 patients with RA, RA with sideroblasts, RAEB, RAEB-t, or CMML seen here between January 1, 1985 (an arbitrarily selected date) and December 31, 1990.

Table 1 compares the 219 M.D. Anderson patients with the 816 patients who formed the basis for the IPSS; the latter patients' characteristics are described in Table 1 of Greenberg et al's report. Our definitions of ''cytopenia'' and of cytogenetic group (''good,'' ''intermediate,'' ''poor'') were chosen to correspond with the definitions of Greenberg et al. The M.D. Anderson patients were younger, but more often had RAEB-t, 2 to 3 cytopenias, and prognostically poor cytogenetics. Given that percent of marrow blasts (21% to 30% least favorable), karyotype, and number of cytopenias (2 to 3 least favorable) determine the IPSS, our patients less often had ''low'' and ''intermediate-1'' (INT-1) IPSS scores and more often had INT-2 or ''high'' scores, the latter associated with the worst prognoses.

Table 1. Comparison of IPSS and M.D. Anderson Patients

	IPSS	M.D. Anderson	*P* Value
Patients	816	219	
Median age*	69	65	
RA/RAS (%)	51	45	.08
RAEB (%)	26	28	.41
RAEB-t (%)	7	24	<.001
CMML (%)	15	3	<.001
Median platelet count/neutrophil count/hemoglobin†	>100/>1.5	72/0.9/9.6	
2-3 Cytopenias (%)	42	66	<.001
Cyto good (%)	70	55	<.001
Cyto inter (%)	14	17	.23
Cyto poor (%)	16	28	<.001
IPSS score			
Low (%)	33	13	<.001
INT-1 (%)	38	41	.56
INT-2 (%)	22	30	.008
High (%)	7	16	<.001

* % of patients age >60 years 75% *v* 65% in the IPSS and MDA groups, respectively ($P = .005$).

† % of patients with platelet count < 100 37% *v* 63% in the IPSS and MDA groups, respectively ($P < .001$). % of patients with neutrophil count <1.5 46% *v* 65% in the IPSS and MDA groups, respectively ($P < .001$). % of patients with Hg <10 54% *v* 60% in the IPSS and MDA groups, respectively ($P = .11$).

Despite the very different nature of the IPSS and the M.D. Anderson patients, the IPSS stratified our patients effectively (Fig 1). However, within the IPSS categories of low, INT-1, and INT-2, probability of survival appeared less in the M.D. Anderson than in the Greenberg et al patients (Table 2); the survival percentiles for the Greenberg et al patients were derived from Fig 6a and Table 4 of their report. Although we did not formally compare our survival data with those of Greenberg et al, the differences appeared noteworthy (eg, median survivals of 2.1 and 1.2 years in our low and INT-1 patients versus 5.7 and 3.5 years in those of Greenberg et al) and unlikely to occur by chance, at least in the INT-1 category in which 89 of our patients were classified. Greenberg et al noted that, independent of the IPSS score, patients over age 60 years had shorter survival than younger patients. However, the survival expectation of our patients in the low, INT-1, and INT-2 categories was worse than the corresponding IPSS patients even if attention was restricted to those IPSS patients over age 60 (or 70) years (Fig 7a, Table 4 of the Greenberg et al report).

We considered four possible explanations for the discrepant outcomes in M.D. Anderson and IPSS patients. First, our patients may have been referred later in the course of their illness. Factors weighing against this possibility are the relatively short intervals between M.D. Anderson presentation and initial documentation of anemia (median, 4.0 months), thrombopenia (median, 1.0 month), or neutropenia (median, 0.5 months). Second, our therapies may have adversely affected our patients' prognoses. However, the therapies given to our patients are not known to have such effects; these therapies included biologic response modifiers, principally GM-CSF and/or erythropoietin, 52%; transfusions, 30%; and low-dose oral chemotherapy similar to that described by Greenberg et al, 18%. Third, blood counts may have been lower in our patients, as suggested by Table 1. Greenberg et al indicate only the proportions of all 894 patients who had a platelet count below 100,000, a neutrophil count below 1,500, or a hemoglobin level below 10, but do not provide this information separately for the low, INT-1, INT-2, and high categories. Perhaps more important they do not provide information indicating that the relationship between blood count and outcome is best described by dichotomizing blood count as they did, rather than by considering a different relationship, eg, one in which the lower the blood count the worse the outcome. Finally, our patients and those of Greenberg et al may have differed in ways that remain to be defined.