

Risk of Myelodysplastic Syndrome and Acute Myeloid Leukemia in Congenital Neutropenias

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Granulocyte colony-stimulating factor (G-CSF) has had a major impact on the management of "severe chronic neutropenia" (SCN), a collective term referring to congenital, idiopathic, or cyclic neutropenia. Almost all patients respond to G-CSF with increased neutrophils, reduced infections, and improved survival. Some responders with congenital neutropenia and Shwachman-Diamond syndrome (SDS) have developed myelodysplastic syndrome and acute myeloid leukemia (MDS/AML), which raises the question of the role of G-CSF in pathogenesis. The issue is complicated because both disorders have a propensity for MDS or AML as part of their natural history. To address this, the Severe Chronic Neutropenia International Registry (SCNIR) used its large database of chronic neutropenia patients treated with G-CSF to determine the incidence of malignant myeloid transformation in the two disorders, and its relationship to treatment and to other patient characteristics. No statistically significant relationships were found between age at onset of MDS or AML and patient gender, G-CSF dose, or duration of G-CSF therapy. What was observed, however, was the multistep acquisition of aberrant cellular genetic changes in marrow cells from patients who transformed, including activating *ras* oncogene mutations, clonal cytogenetic abnormalities, and G-CSF receptor mutations. In murine models, the latter produces a hyperproliferative response to G-CSF, confers resistance to apoptosis, and enhances cell survival. Since congenital neutropenia and SDS are inherited forms of bone marrow failure, G-CSF may accelerate the propensity for MDS/AML in the genetically altered stem and progenitor cells, especially in those with G-CSF receptor and *ras* mutations (82% and 50% of patients who transform, respectively). Alternatively, and equally plausible, G-CSF may simply be an "innocent bystander" that corrects neutropenia, prolongs patient survival, and allows time for the malignant predisposition to declare itself. In patients who transform to overt MDS or AML, hematopoietic stem cell transplantation is the only chance for cure. In those with "soft" signs of MDS, such as an isolated clonal cytogenetic change but without other evidence of MDS, or with an isolated G-CSF receptor mutation, there is room for conservative management. One option is to reduce the G-CSF dosage as much as possible, and observe the tempo of progression, if any, to more overt signs of malignancy.

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SEVERE CHRONIC NEUTROPENIA (SCN) refers to a heterogeneous group of disorders of myelopoiesis that encompasses cyclic neutropenia, idiopathic neutropenia, and congenital neutropenia. All of these disorders are characterized by absolute neutrophil counts of less than $0.5 \times 10^9/L$ on three separate occasions during 6 months of observation. Kostmann's syndrome, a subtype of congenital neutropenia inherited in an autosomal-recessive manner, is characterized by onset in early childhood of profound neutropenia, recurrent life-threatening infections, and a characteristic "maturation arrest" of bone marrow myeloid precursors at the promyelocyte-myelocyte stage of differentiation.^{22,23}

"Congenital neutropenia" as used here has the

same hematologic phenotype and clinical presentation as Kostmann's syndrome. Neutropenia is profound, with counts usually less than $0.2 \times 10^9/L$, and often absolute. The recessive autosomal inheritance of Kostmann's syndrome is deduced by inference when there is more than one affected child in a family. Congenital neutropenia is the more appropriate designation used for a single sporadic case in a family, which may or may not be inherited in an autosomal-recessive manner. It is now apparent that most patients with congenital neutropenia have heterozygous mutations in the gene encoding neutrophil elastase,³ and problems with definitions and terminology will resolve when the molecular basis for these disorders becomes clear. This was recently underscored with the discovery of a novel point mutation in the extracellular domain of the G-CSF receptor in a sporadic case of congenital neutropenia hyporesponsive to G-CSF treatment.^{9,36} Until all of these molecular pathogenetic mechanisms are known, the option to combine or split the two disorders remains open. For this report, the terms Kostmann's syndrome and congenital neutropenia are used interchangeably.

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Shwachman-Diamond syndrome (SDS)³⁰ is an additional and discrete subtype of congenital neutropenia. A recent segregation analysis of 84 patients with SDS provided strong evidence for its inheritance in an autosomal-recessive manner.¹³ Essential for the diagnosis are neutropenia of variable severity, often with other cytopenias, and exocrine pancreatic dysfunction; supportive features of SDS are short stature, skeletal abnormalities, and abnormal liver function tests.¹⁴ The SDS locus maps to the centromeric region of chromosome 7 (7p12-q11).¹⁵ SDS marrow cells show abnormally increased apoptosis mediated through the *fas* pathway,⁷ and SDS patients also have a serious generalized marrow dysfunction with abnormal bone marrow stroma in terms of its ability to support and maintain hematopoiesis.⁸

Myelodysplasia and Leukemic Transformation

Historically, congenital neutropenia and SDS were classified with other inherited marrow failure syndromes as "benign hematology" in order to contrast sharply with hematologic cancer. Patients with Fanconi's anemia, congenital amegakaryocytic thrombocytopenia, Diamond-Blackfan anemia, congenital neutropenia, and SDS often died early in life from complications of pancytopenia. If they survived long enough, however, it became obvious that these benign disorders conferred an inordinately high predisposition to the spontaneous development of myelodysplastic syndrome and/or acute myeloid leukemia (termed MDS/AML herein for ease of discussion but not to imply that they are always the same disease).

What is the basis for this predisposition? Carcinogenesis occurs as a sequence of events that is driven by genetic damage and by epigenetic changes. In the traditional view, the initiation of cancer starts in a normal cell through mutations from exposure to carcinogens. In the promotion phase that follows, the genetically altered, initiated cell undergoes selective clonal expansion that enhances the probability of additional damage from endogenous mutations of DNA-damaging agents. Finally, during cancer progression, malignant cells show phenotypic changes, gene amplification, chromosomal alterations, and altered gene expression.

Our hypothesis is that in the inherited marrow failure syndromes, the first "hit" or cancer-initiating step may be the germline genetic abnormality itself that initially manifests as the single-lineage or multiple-lineage myelopathy. The predisposed progenitor, already initiated, could conceptually show decreased responsiveness to the signals that regulate homeostatic growth, terminal cell differentiation, or programmed cell death. The leukemic promotion and progression steps leading to MDS/AML could then

ensue readily in the initiated pool of progenitors or stem cells.

With respect to congenital neutropenia, there have been three case reports of patients who developed AML prior to the use of hematopoietic growth factors,^{12,27,29} and one more recent patient diagnosed with acute leukemia prior to starting G-CSF.³⁹ Because most patients with congenital leukemia died at a young age from bacterial sepsis or pneumonia in the pre-cytokine era, the true risk of patients with congenital neutropenia developing MDS/AML was not clearly defined. However, there were 128 cases of congenital neutropenia reported through 1989, which is the first year that G-CSF was available for general use, leading to a crude estimated risk of leukemia of 2%. Of approximately 200 patients reported through 2000 who did not receive G-CSF, four had leukemia (2%).¹

In SDS, the degree of neutropenia is usually less severe than in congenital neutropenia and most patients survive the childhood years. The crude rate for MDS or acute leukemia in patients with SDS was 8% in one case series (seven of 88 patients)¹⁴ and 33% in a smaller case series (seven of 21).³¹ It was 5% in approximately 200 SDS cases reported in the literature prior to 1990, and 10% in more than 300 patients who had not received G-CSF reported through 2000.¹

This predisposition to hematologic malignancy is confined to congenital neutropenia and SDS and has not been observed in other severe chronic neutropenias, such as glycogen storage disease type 1b, cyclic neutropenia, or idiopathic neutropenia.

G-CSF and the Severe Chronic Neutropenia International Registry

In 1987, clinical trials were started to test the utility of recombinant human G-CSF therapy for SCN. The efficacy was demonstrated immediately because more than 90% of the total group of patients with idiopathic, cyclic, and congenital forms of neutropenia showed a selective, sustained increase in neutrophil numbers.² This set the stage for long-term administration of G-CSF for these disorders.

Shortly after G-CSF was acknowledged as first-line therapy for SCN, the first³⁷ of several reports surfaced on the development of MDS/AML in patients with congenital neutropenia and SDS who were receiving the recombinant cytokine. The cases were compiled by Kalra et al²¹ who reported on 13 patients receiving G-CSF (12 with Kostmann's syndrome or congenital neutropenia, and one with SDS) who had overt transformation, and an additional patient with SDS who developed a clonal cytogenetic abnormality of marrow cells but without MDS/AML. A review of all cases of congenital neutropenia treated with G-CSF and

reported in the literature identified 23 of 101 patients in whom MDS and/or AML occurred (a 23% crude risk). Among the SDS reports, four of 12 who received G-CSF developed leukemia.¹

In response to the obvious need to capture detailed data on these and other patients receiving long-term G-CSF therapy, the Severe Chronic Neutropenia International Registry (SCNIR) was established in 1994 to continue monitoring the clinical course, treatment, and disease outcomes of patients with SCN. Clinical trial data from 1987 to 1994 were retrospectively transferred to the Registry and were added to the data of newly diagnosed SCN patients from 1994 onward. The SCNIR is a unique resource that continues to collect clinical data on large numbers of patients worldwide. Patient data are submitted internationally to the coordinating centers at the University of Washington, Seattle, and the Medizinische Hochschule, Hannover, Germany. As of January 1, 2001, the following numbers of patients were enrolled in the SCNIR: 383 with congenital forms of neutropenia including 26 with SDS, 160 with cyclic neutropenia, and 288 with idiopathic neutropenia.

Malignant Myeloid Transformation From the SCNIR Database

In 1996 and 1997, the SCNIR tabled its first report on patients with congenital neutropenia on G-CSF therapy who developed MDS/AML.¹¹ Of 249 patients at risk, 23 underwent malignant transformation, for a crude rate of about 9%. Since those reports, there has been progressive enrollment of new patients into the SCNIR from North America, Europe, and Australia; there has also been in parallel an annual accrual of new patients with congenital neutropenia and SDS on G-CSF that evolved into MDS/AML. As of January 1, 2001, there were 48 patients with MDS/AML of the 383 patients with congenital forms of neutropenia in the SCNIR (crude rate, about 12.5%). Two of 26 who had SDS transformed, as did 46 of 357 who had congenital neutropenia. There are no cohort data prior to the use of G-CSF. Comparison of literature reports with the SCNIR data of congenital neutropenia patients for whom G-CSF was not used suggests a significantly increased risk of transformation with G-CSF (4 of 200 cases without G-CSF v 46 of 357 with G-CSF; $P < .01$). The number of SDS cases in the SCNIR is relatively low, and comparison with the literature is less meaningful (34 of 324 cases without G-CSF v 2 of 26 with G-CSF; not significant).

To determine if the incidence of MDS/AML in the SCNIR patients was related to G-CSF dosage or duration of therapy, or to other patient demographics, a detailed analysis was conducted on data received up to December 31, 1998 on 352 patients with congenital neutropenia treated with G-CSF.¹⁰ Of these, 31

developed MDS/AML for a crude rate of transformation of nearly 9%. For each yearly treatment interval, the annual rate of MDS/AML development was less than 2%. No statistically significant relationships were found between age at onset of MDS/AML and patient gender, G-CSF dose, or duration of treatment. The bone marrow studies of nine additional patients showed cytogenetic clonal changes, but the patients had not transformed to MDS/AML. Thus, the data did not support a cause-and-effect relationship between the development of MDS/AML and G-CSF therapy or other descriptors. However, a direct contribution of G-CSF in the pathogenesis of the malignancy could not be excluded (see below).

Aberrant Cellular Genetic Changes

Conversion to MDS/AML in congenital neutropenia patients receiving G-CSF is associated with one or more cellular genetic abnormalities that provide insight into the pathobiology of the transformation, and which may be useful in identifying patients who are at high risk. The cellular genetic changes are acquired after starting G-CSF and occur singly or in combinations. Remarkably, the abnormalities have predictably similar characteristics in most patients and underscore a fairly specific multistep pathogenesis in the evolution into MDS/AML (Table 1). The information in Table 1 was compiled from unpublished research data in the SCNIR and from the published sources indicated. As summarized, almost all patients with congenital neutropenia (but not with SDS) have inherited a heterozygous mutation in the gene encoding neutrophil elastase which likely accounts for the disorder.³ At varying timepoints after starting G-CSF therapy, about half of the congenital neutropenia patients who transform acquire the same activating *ras* oncogene mutation, namely a GGT (glycine) to GAT (aspartic acid) substitution at codon 12.²¹ Almost all patients who transform also show an acquired cytogenetic clonal alteration in bone marrow cells, usually -7 or 7q-, but also +21.^{10,11,21,37} Occasionally both chromosome abnor-

Table 1. Abnormal Cellular Genetic Changes That Characterize the Multistep Pathogenesis of MDS/AML in Patients With Congenital Neutropenia Taking G-CSF Who Transform

Abnormality	Patients Affected*
Neutrophil elastase mutation ³	90%
<i>ras</i> oncogene mutation ²¹	50%
-7 or 7q-, +21, other ^{11,10,21,37}	>90%
G-CSF-R mutation ^{4-6,20,32-34,38}	82%
MDS/AML	Likely 100%

* The percentage of patients affected with each cellular genetic abnormality was compiled from unpublished research data in the SCNIR, and from published sources as indicated.

malities occur in the same cell. Most patients also develop one or more G-CSF receptor point mutations. These nonsense mutations result in the truncation of the C-terminal cytoplasmic region, a subdomain that is crucial for G-CSF induced maturation.^{4-6,33,34} The acquired mutation is directly operative in the conversion to MDS/AML. In murine models, the mutation results in impaired ligand internalization, defective receptor downmodulation, and enhanced growth signaling that produces an exaggerated hyperproliferative effect in response to G-CSF.^{16,17,19,35} This also confers resistance to apoptosis and enhances cell survival¹⁸ that favors clonal expansion *in vivo*.¹⁷ The clinical interplay between G-CSF and the receptor mutation was underscored in the report of a patient with congenital neutropenia on G-CSF who developed the receptor mutation and AML.²⁰ When G-CSF was stopped, the blast count in blood and in marrow fell to undetectable levels on two occasions without giving chemotherapy, although the mutant receptor was persistently detectable during the remissions.

Do all patients with the G-CSF receptor mutation develop MDS/AML? The likely answer is "yes," although some congenital neutropenia patients taking G-CSF have acquired the receptor mutation but not yet developed MDS/AML.^{6,32,38} Obviously, these patients are at high risk and are being monitored closely.

Role of G-CSF in the Malignant Conversion

Because there is no definitive evidence that the dose of G-CSF or the duration of G-CSF therapy are directly related to malignant transformation, G-CSF may simply be an "innocent bystander" that corrects the neutropenia, prolongs patient survival, and allows time for the malignant predisposition to declare itself. Alternatively, and equally plausible, G-CSF may accelerate the propensity for MDS/AML in the genetically altered stem and progenitor cells in congenital neutropenia and in SDS. G-CSF may rescue malignant clones that would otherwise be destined for apoptosis. An axiom of oncogenesis is that rapidly dividing cells are more susceptible to mutational events. Since therapeutic G-CSF provides a powerful proliferative signal for marrow cells, it is a reasonable hypothesis that congenital neutropenia and SDS marrow progenitors acquire new mutations. From the evidence cited herein, acquisition of a G-CSF receptor mutation in the face of therapeutic G-CSF in congenital neutropenia can provide the hyper-responsive replicative scenario that can relentlessly evolve into MDS/AML. Finally, is recombinant human G-CSF a carcinogen? This would seem highly unlikely. As a physiologic regulator of hematopoiesis, it would be unexpected for G-CSF to break molecular bonds and cause DNA damage, even when used in

therapeutic dosages. It is noteworthy that MDS/AML has not been seen in other SCN patients on long-term G-CSF therapy.

Treatment of MDS and AML

G-CSF has been used for 14 years to treat SCN. The neutrophil responses have been overwhelmingly positive and consistent and, hence, G-CSF is still deemed specific therapy for all of these disorders⁴⁰ with a high margin of safety.¹¹ For patients with congenital neutropenia and SDS, routine blood counts every 3 to 6 months and annual bone marrow testing for morphology and cytogenetics are recommended in order to detect malignant change early.

The diagnosis of overt AML with more than 30% blasts in the marrow, or of MDS with 5% to 30% blasts in the marrow with or without a clonal cytogenetic marker, requires a prompt, aggressive course of action. G-CSF should be stopped to determine if a spontaneous remission will ensue.²⁰ Since there are no survivors in the SCNIR database among patients treated with supportive care only, transretinoic acid alone, or chemotherapy alone, the only chance for cure is by a hematopoietic stem cell transplant. Family members should be tissue-typed at once and if no suitable donor is identified a search should be initiated for a matched unrelated donor or for a closely matched umbilical cord blood specimen. To date, the outcome of transplantation for these patients has been poor, with only three survivors of 18 cases transplanted.⁴¹ In contrast, nine of 11 congenital neutropenia patients survived, and eight appeared cured when transplanted for reasons other than malignant transformation.⁴¹ Causes of transplant failures in the MDS/AML group varied and included the use of mismatched donors, progressive refractory AML, illness at the time of procedure, and transplantations performed in desperation. The poor results are also consistent with other reports of patients who develop MDS/AML arising in the context of other inherited predispositions to leukemia.^{24,25,28}

The discovery of an isolated marrow clonal cytogenetic abnormality without other evidence of MDS or AML in patients with congenital neutropenia or SDS raises management issues. One option is to perform a hematopoietic stem cell transplantation if there is a donor as soon as feasible. The *a priori* argument is that the chance for cure is higher when the patient is well and with a low burden of malignancy. The problem with this decision centers on not knowing the tempo of progression from the cytogenetic change to clearcut MDS or AML. The SCNIR has data on three patients with congenital neutropenia, 2 with SDS, two with idiopathic neutropenia, and two with cyclic neutropenia or a variant, whose marrows show cytogenetic clonal changes but without malignant transformation. Three of the nine patients have

abnormalities of chromosome 7; the other changes are variable and show no consistent pattern. These patients have been observed for 34 to 86 months after the initial abnormal clonal change was detected and no progression has been seen.

Thus, there may not be a need to rush to transplant in all patients. Instead, one recommendation is to lower the G-CSF to the lowest dose that maintains neutrophil counts greater than $0.5 \times 10^9/L$ and to monitor the patient regularly for change. This approach is especially true in SDS. One of us (M.H.F.) has performed serial marrow testing for 5 years on a SDS patient with *i(7q)* and there has been no progression to MDS/AML and no deterioration in marrow function. It is also noteworthy that eight children with MDS (four *de novo*, four treatment-related) associated with -7 or $7q-$ have achieved spontaneous hematologic and cytogenetic remission; seven of these remissions were durable.²⁶

Opinions will vary about the best way to manage patients with clonal disease but without overt hematologic malignancy. Clonal disease also includes acquisition of a G-CSF receptor mutation or an activating *ras* oncogene mutation in marrow from a patient with congenital neutropenia taking G-CSF who shows no other signs of MDS or AML. In one such patient with an isolated G-CSF receptor mutation, a hematopoietic stem cell transplant was performed to eliminate the risk of leukemic conversion.⁴¹ Debate about this controversial form of management remains open, and watchful waiting is an acceptable option.

G-CSF has a clear therapeutic role in the management of severe chronic neutropenia. Its role in hematopoietic malignant transformation is less clear, but suspect, at least in congenital neutropenia. Only careful long-term follow-up of the cohort of patients receiving this treatment will provide the answer.

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