Risk and Benefit of Treatment of Severe Chronic Neutropenia With Granulocyte Colony-Stimulating Factor

Tammy E. Cottle, Carol J. Fier, Jean Donadieu, and Sally E. Kinsey

The Severe Chronic Neutropenia International Registry (SCNIR) was established in 1994 following four phase I/II and one phase III clinical trial on the use of filgrastim (recombinant human granulocyte colony-stimulating factor [r-metHuG-CSF]) as a treatment for severe chronic neutropenia (SCN). A primary purpose of the SCNIR is to monitor SCN patients treated with filgrastim for adverse events that might occur over time. As of December 31, 2000, 832 patients with SCN (384 congenital, 160 cyclic, 288 idiopathic) were enrolled. Clinical trial and Registry data show that filgrastim is an effective treatment for SCN; more than 90% of patients treated respond with normalization of blood neutrophil counts. The SCNIR has collected data on bone pain, splenomegaly, hepatomegaly, thrombocytopenia, osteopenia/osteoporosis, vasculitis, glomerulonephritis, growth and development, pregnancy and fertility, leukemic transformation, and mortality. Analysis of data from patients who received filgrastim for up to 11 years did not identify any adverse events associated with increased duration of treatment.

PRIOR TO THE AVAILABILITY of the hematopoietic growth factors there was no predictably effective therapy for severe chronic neutropenia (SCN). The mainstays of care were careful observation and prompt antibiotic treatment. Historically, a variety of agents were given short term without apparent benefit, including glucocorticosteroids, lithium salts, gammaglobulin preparations, immunosuppressive drugs, and even splenectomy. All proved either ineffective or unsuitable for long–term therapy, although bone marrow transplantation has been successful in a few patients with congenital neutropenia.[18,27]

This general lack of long-term efficacy and the observation that filgrastim (recombinant human granulocyte colony-stimulating factor [r-metHuG-CSF]; Neupogen, Amgen, Thousand Oaks, CA) selectively stimulated neutrophil production[21,22] led in 1987 to the initiation of clinical trials of filgrastim for the treatment of SCN. Four phase I/II trials and one phase III trial were conducted.[1,3,10,13,14,25] The phase I/II trials provided initial safety and efficacy data for filgrastim treatment of congenital, cyclic, and idiopathic neutropenia. The phase III trial was designed to confirm these findings in a multicenter, randomized, controlled trial of the three subtypes of SCN combined.[10] Patients were required to be at least 6 months of age and to have a history of significant infections, and either documented severe neutropenia with at least three absolute neutrophil counts (ANC) of less than 0.5×10^9/L in the previous 6-month period, or regular neutrophil cycles with 5 consecutive days of an ANC less than 0.5×10^9/L during each cycle. The results confirmed the findings of the previous studies.[1,5,26] The median age of the 123 patients evaluated was 12 years (range, 1 to 76). One hundred eight of the 120 patients who received filgrastim had a complete response (median ANC $> 1.5 \times 10^9$/L) and four additional patients achieved partial responses (median ANC $> 0.5 \times 10^9$/L but $< 1.5 \times 10^9$/L). Mouth ulcers, presumed infections (defined as inflammatory symptoms treated with antibiotics), and total antibiotic use all decreased significantly.

These phase I/II and III trials indicated that filgrastim effectively elevated the ANC and reduce or eliminate signs and symptoms of illness in most SCN patients. In this setting of rare but heterogeneous syndromes, where little historical data existed about the clinical disease course, it was well recognized that these clinical trials served as the first formal mechanism of comprehensive data collection for this group and that this new treatment option could also lead to the identification of many new patients as well as allow for the evaluation of long-term treatment that had not been addressed by the clinical trials.

Recognizing this need for more information, the Severe Chronic Neutropenia International Registry (SCNIR) was established in 1994 through collabora-

From the Severe Chronic Neutropenia International Registry, Department of Medicine, School of Medicine, University of Washington, Seattle, WA.

The Severe Chronic Neutropenia International Registry is supported by Amgen, Inc.

Address reprint requests to Tammy E. Cottle, Severe Chronic Neutropenia International Registry, Plaza 600 Building, 600 Stewart St, Ste 1503, Seattle, WA 98101.

0037-1963/02/3902-0004$35.00/0
doi:10.1053/shem.2002.31914

tion with many diverse groups and the support and funding of Amgen. During the first 6 years, one of the primary objectives of the Registry was to monitor and assess the long-term response and safety of primary treatments in SCN patients. Registry data allowed comparison and refinement of safety data collected during the clinical trials and provided a means to monitor new events potentially related to long-term filgrastim therapy. Whereas the clinical trials were conducted according to rigorous protocols that specified inclusion and exclusion criteria as well as the filgrastim treatment and monitoring regimens, the SCNIR was intended to capture data on a larger number of patients in a treating-physician setting. Therefore, the Registry protocol was written to provide guidelines as suggested by the Advisory Board but there were no requirements for the treatment or monitoring of patients. The Registry has been able to collect a large number of internationally dispersed cases and capture data from patients who have now received filgrastim for as long as 11 years.

The Registry has offices for centralized collection and analysis of data in Seattle, WA and Hannover, Germany; activities are overseen by an Advisory Board of expert physicians from Australia, Europe, and North America. In addition to the collection and dissemination of clinical data, the Registry has become a unique resource to facilitate research on the genetic, molecular, and cellular mechanisms for SCN.

French SCN Registry

The French Registry was organized independently from the SCNIR in 1994 but operated under a similar protocol with the same inclusion and exclusion criteria. In 2001, it was agreed to merge the French Registry with the SCNIR. While the two databases have not yet been consolidated, data from the French Registry generally support the conclusions of the SCNIR reported here while contributing some interesting cases.

With a tradition of centralized record keeping in France, the French Registry has successfully accrued most identified SCN cases. By March 2001, 196 patients had been registered (136 congenital, 42 cyclic, 18 idiopathic). G-CSF was clearly effective in 94 of 105 patients. Apart from the risks of leukemia and osteoporosis, adverse events were transient, relatively moderate, and consistent with those reported by the SCNIR. Twelve cases of malignant transformation were diagnosed by cytologic examination, including four in which G-CSF had been administered. In addition, there was one case of renal carcinoma in a patient with glycogen storage disease type 1b (GSD1b), suggesting the need for yearly monitoring by renal sonogram. Fifteen deaths were reported to the French Registry (14 with congenital neutropenia, including six with Kostmann's syndrome and four with Shwachman-Diamond syndrome; and one with cyclic neutropenia). None of the deaths was directly attributable to G-CSF treatment and five were due to complications secondary to acute myelogenous leukemia (AML) or myelodysplasia (MDS), including the four cases in which G-CSF was administered.[11,12]

Registry Background

Initial enrollment in the SCNIR consisted of the patients who participated in the clinical trials and were continuing long-term treatment with G-CSF. Enrollment for new patients required documentation of findings indicative of SCN including a history of recurrent, significant infections, an ANC of less than 0.5×10^9/L on at least three occasions in 3 months, bone marrow aspirate consistent with SCN, and cytogenetic evaluation. All patients signed a release of medical information prior to registration. As of December 31, 2000, 832 patients with SCN (384 congenital, 160 cyclic, 288 idiopathic) have been entered.

Prior to enrollment, treating physicians were required to submit medical information to confirm the patient's diagnosis and to establish a baseline history. Enrollment forms for each patient were then reviewed and approved by an Advisory Board physician. Subsequent to registration, data collection forms were mailed to treating physicians on a biannual basis during the first 6 years of the Registry operation and annually starting in 2000. Forms were completed by the physician and returned to the Registry on a voluntary basis. Data are maintained in a longitudinal database using Medlog (Information Analysis Corp, Incline Village, NV), and SAS (SAS Institute, Cary, NC) is used for data analysis. Data are analyzed yearly and reported to regulatory authorities and summarized to participating physicians. The last data analysis was performed on 731 patients enrolled as of December 31, 1999 (634 patients with postregistration data were evaluable). The remainder of this report will focus on the comparison of treatment and safety data collected during the clinical trials with that of the Registry.

Hematopoietic Response to Filgrastim Treatment

The goal of treatment of SCN with filgrastim is to reduce or prevent infections and symptoms of inflammation, predictably achieved by raising the blood neutrophil count to a normal level. The dose and schedule of filgrastim needed for response greatly vary. Statistics for the median daily dose for all patients by diagnosis (maximum duration of 11 years)

Table 1. Median Filgrastim Dose in Phase III Clinical Trials (at time of initial response) compared to Registry Data (overall use)

	Congenital SCN		Cyclic SCN		Idiopathic SCN	
Filgrastim Dose (μg/kg/d)	Phase III Clinical Trial (n = 49)	SCNIR (n = 287)	Phase III Clinical Trial (n = 20)	SCNIR (n = 122)	Phase III Clinical Trial (n = 39)	SCNIR (n = 177)
Median	11.5	5.8	5.75	2.1	3.45	1.1
Range	3.45-23	0.0-240.0	1.0-6.0	0.0-11.2	1-5.75	0.0-32.09

are shown in Table 1. Patients with well-documented idiopathic or cyclic neutropenia generally require substantially lower doses than patients with congenital neutropenia. For a patient not previously treated with filgrastim, a good plan is to begin with the median dose shown in Table 1 and then to titrate the dose up or down at 1- to 2-week intervals until the lowest dose effecting a response is achieved. Alternate-day or thrice-weekly treatment is often effective for patients responding to low doses of daily therapy.[15] Patients who fail to respond to $\geq$100 μg/kg/d of G-CSF should be considered as candidates for bone marrow transplant.[23]

In the randomized clinical trial more than 90% of patients treated with filgrastim showed normalization of blood neutrophil counts.[24] Registry data suggest an even higher proportion of patients respond, but there are still exceptions, particularly in the congenital subtype.[2,9,19,20] A good initial rise usually predicts good long-term improvement as well. Loss of response with time through "marrow exhaustion" or other changes has not been an observed effect with long-term therapy. The effects of filgrastim on median leukocyte, neutrophil, hemoglobin, and platelet values over a 10-year treatment period are listed in Table 2. Hemoglobin tends to rise with time, probably due to increased endogenous erythropoietin with reduced chronic inflammation, and leads to the improvement in general well-being. Platelets decline from abnormally elevated counts, probably due to chronic inflammation associated with untreated infections, to normal counts during the first year of treatment. Thereafter, platelets usually remain within the normal range, as observed in the randomized trial. In general, so long as the patient's health status is otherwise unchanged, blood counts are relatively stable on a fixed dose of filgrastim. Monthly or bimonthly monitoring of blood cell counts is satisfactory for patients on long-term therapy.

Safety Data

Registry follow-up forms gather information regarding safety and side effects. The SCNIR data collection forms were intended to capture events that were of potential concern during the clinical trials, as well as to identify new trends with long-term treatment. Table 3 compares the side effects observed in the initial clinical trial with SCNIR and French Registry data.

Bone Pain

Many patients beginning filgrastim for SCN experience bone pain, headache, and musculoskeletal symptoms, attributable to the expansion of hematopoietic tissues as a direct effect of treatment and predictably declining with continued therapy. These symptoms are usually managed with acetaminophen or other mild analgesics.

Splenomegaly/Hepatomegaly

Splenic enlargement is frequently present at pretreatment baseline in SCN patients and is commonly seen

Table 2. Hematological Data

	Mean ANC ($\times 10^9$/L)				Mean Hemoglobin (g/dL)				Mean Platelets ($\times 10^9$/L)				Mean WBC ($\times 10^9$/L)			
	Congenital	Cyclic	Idiopathic	Total	Congenital	Cyclic	Idiopathic	Total	Congenital	Cyclic	Idiopathic	Total	Congenital	Cyclic	Idiopathic	Total
Pre-drug	0.22	0.56	0.39	0.34	11.02	11.68	12.25	11.55	422.02	335.66	282.11	360.64	6.38	4.66	3.44	5.10
0-1 yr	2.88	5.48	3.84	3.70	11.26	11.93	12.42	11.74	286.70	292.81	257.84	279.20	10.32	10.12	7.33	9.37
1-2 yr	2.88	4.54	4.28	3.63	11.67	12.35	12.81	12.14	269.65	271.37	241.60	261.78	9.11	8.82	7.26	8.51
2-3 yr	2.86	4.90	4.22	3.66	11.88	12.62	13.04	12.36	260.37	273.74	230.13	254.62	8.17	9.27	6.98	8.06
3-4 yr	2.83	4.34	4.70	3.70	12.08	12.53	12.96	12.43	253.17	283.07	227.97	252.80	7.81	8.37	7.51	7.85
4-5 yr	2.57	4.19	4.22	3.32	12.14	12.76	12.87	12.45	243.59	270.58	221.88	244.01	7.21	8.28	6.97	7.38
5-6 yr	3.25	4.87	4.50	3.88	12.35	12.73	12.94	12.56	246.92	244.30	218.18	240.00	7.64	8.44	7.41	7.76
6-7 yr	3.40	5.02	5.27	4.10	12.20	12.94	12.96	12.51	239.97	249.91	223.80	238.75	7.27	8.98	8.79	7.94
7-8 yr	2.91	4.00	6.09	3.72	12.32	12.88	13.26	12.61	233.13	247.61	222.80	234.29	6.97	7.90	8.41	7.42
8-9 yr	2.68	5.86	5.19	3.73	12.35	12.67	13.36	12.59	220.95	249.58	203.69	223.83	6.52	9.74	7.75	7.38
9-10 yr	3.00	4.60	5.87	4.03	12.56	12.88	12.97	12.73	225.81	242.53	225.61	229.74	7.09	8.07	9.10	7.78
10-11 yr	1.82	4.28	8.17	3.23	12.57	12.92	12.85	12.71	243.13	245.75	241.13	243.73	5.97	8.47	10.24	7.18

Abbreviations: ANC, absolute neutrophil count; WBC, white blood cell count.

Table 3. Comparison of Incidence of Specific Events Reported

	Clinical Trial (n = 197)	SCNIR (n = 634)*	French Registry (n = 196)
Splenomegaly			
Baseline	15%	15.1%	6%
Highest rate on treatment	31%	31.8%	15%
Thrombocytopenia (platelets $<50{,}000/\mu L$)	6%	4.1%	5%
Osteoporosis/osteopenia	9.6%	17.4%†	19%†
Vasculitis	2.0%	4.1%	2%
Urinary abnormalities (sustained and new onset)	2.0%	2.0%	5%

* Number of Registry patients with postregistration data.

† Includes asymptomatic cases in which abnormal bone density was the only finding; bone density evaluations were not done as part of the clinical trials.

early in the course of treatment with filgrastim. The clinical trials monitored spleen size by physical examination and the phase III trial by imaging studies. Palpable splenomegaly was reported at baseline in 15% of study patients and in 30% of patients on filgrastim. When used, computed tomography or magnetic resonance imaging showed a median increase in spleen volume of 38% over the first 5 months of filgrastim treatment (range, 2% to 148%). Spleen volume then tended to plateau at 18 months and at approximately 2.5 years had decreased toward pretreatment values.

Registry data confirmed the common finding of pretreatment splenomegaly, reported at baseline in 18% of patients with congenital neutropenia. During the first year of filgrastim therapy, the prevalence increased to 38.2% and remained near this level (27% to 45%) through 10 years of therapy. The maximum prevalence rate among patients with cyclic and idiopathic neutropenia was not as high either at baseline (13% and 12%, respectively) or during 10 years of filgrastim therapy (18% and 18%, respectively). Splenomegaly can be associated with the underlying disease and its progression, with severe infection, or associated with leukemic transformation.

The prevalence of hepatomegaly among filgrastim-treated Registry patients is less than splenomegaly but similar to the pattern observed in congenital neutropenia. The highest prevalence of palpable hepatomegaly before treatment with filgrastim was seen in patients with congenital neutropenia (21%) with a median liver measurement of 2 cm below costal margin. During the first year of filgrastim therapy, the prevalence increased to 35% and then decreased slightly (ranging from 22% to 29%) through 10 years of therapy. The prevalence of baseline hepatomegaly is much less among patients with cyclic and idiopathic neutropenia (10% and 5%, respectively). These rates increase during the first year of treatment for idiopathic neutropenia (12%) but decrease slightly in patients with cyclic neutropenia (9%). During the subsequent 10 years of treatment, the prevalence of hepatomegaly fluctuates around or below the first year rate with no specific patterns or trends.

Thrombocytopenia

Six percent of patients in the clinical trials, most with a prior history of thrombocytopenia, experienced a further decrease in platelet counts to less than 50×10^9/L. Most were managed by interrupting or reducing the filgrastim dose. Registry data indicate that either the term "thrombocytopenia" and/or a platelet count of less than 50×10^9/L was reported in 4.1% (26/634) of patients; seven were not receiving filgrastim at the time of event onset. Seventeen had congenital, four had cyclic, and five had idiopathic neutropenia. Among the 19 treated patients, seven events occurred concurrently with conversion to or during treatment of MDS/AML. These data continue to support the conclusion that thrombocytopenia remains an infrequent occurrence during treatment with filgrastim (<6%); it was more often seen in patients with congenital types of neutropenia and onset was not related to increased duration of therapy. Most cases of thrombocytopenia were managed with dose reduction or interruption of filgrastim.

Osteopenia/Osteoporosis

Signs and symptoms of osteoporosis include deformity, localized pain, and fracture. The most common deformity is loss of height due to vertebral collapse. Radiological assessment is the principal means of diagnosing osteoporosis.

From the phase I/II and III clinical trials of 197 SCN patients, 19 patients, all with congenital neutropenia, were found to have evidence of osteoporosis/osteopenia. Nine had radiographic evidence of osteopenia (lumbar or wrist) prior to the initiation of filgrastim; the remaining cases were either negative or not evaluated prestudy. The filgrastim dose at onset of osteoporosis/osteopenia ranged from 0.8 to 145 μg/kg/d; in no patient was the drug discontinued due to the event. Bone disorders were not anticipated in this population and therefore routine prescreening for evidence of osteoporosis was not conducted in the clinical trials.

Physicians participating in the SCNIR were encouraged to obtain bone density measurements by any modality for a more accurate and early assessment of potential bone changes, but these diagnostic procedures have been reported in only 32% of patients. In the Registry, either osteopenia or osteoporosis was found in 17% (127/731) of SCNIR patients

(93 congenital, 13 cyclic, 21 idiopathic). Symptoms were not reported for most of these patients and in many cases (n = 46) were based only on abnormal bone density measurements. No correlation was found between filgrastim dose and the development of osteopenia or osteoporosis. Osteoporosis/osteopenia has been documented at baseline in some patients with congenital neutropenia; however, the pathophysiology and any potential relationship to long-term filgrastim treatment remain unknown.

Vasculitis

The SCN clinical trials reported a 3% incidence of cutaneous vasculitis. Lesions were usually limited to the skin, and more than half of these cases were biopsy–proven leukocytoclastic vasculitis. Symptoms of vasculitis generally developed simultaneously with an increase in ANC and abated when the number of neutrophils decreased. Most patients were able to continue filgrastim at the same or a reduced dose. The mechanism of vasculitis in these patients is unknown.

In the SCNIR, vasculitis has been reported in 4.1% of patients; the rate was slightly higher among patients with idiopathic neutropenia (6%) compared to congenital and cyclic neutropenia (3% and 3%, respectively). Some cases of vasculitis predated the initiation of filgrastim. Single episodes were usually associated with a local injury or infection, while patients with multiple or chronic episodes often had other autoimmune-type diagnoses including Sjögren's syndrome, Buerger's disease, common variable immunodeficiency syndrome, Crohn's disease, or T-cell lymphoproliferative disease. Most cases involved only skin, but renal and musculoskeletal systems were also sometimes affected. The majority of patients were able to continue filgrastim at the same or a reduced dose.

Glomerulonephritis

Rare cases of hematuria/proteinuria were observed in the clinical trials. Symptoms were normally either transient and minor, associated with a urinary tract infection, or explained by a pre-existing systemic or renal disease. In the SCNIR it was noted that chronic urinary problems were reported in some patients; a review identified 13 patients (10 congenital, two idiopathic, two cyclic) in whom urinary problems were not attributed to another underlying medical condition. Four of these patients had evidence of urinary symptoms before the initiation of filgrastim; symptoms were reported 0.08 to 7 years after the start of therapy in the remaining patients. Eight of the 13 patients had persistent symptoms over more than 1 year (up to 7.6 years) and six patients were hospitalized either in association or concurrent with the urinary symptoms. Five patients had systemic involvement, including two diagnosed with Henoch-Schönlein purpura, two siblings with cutaneous and hematological symptoms, and one patient with a prior history of systemic vasculitis.

Based on this data review, it appears that patients with congenital neutropenia are predisposed to developing immune complex disease sometimes associated with Henoch-Schönlein purpura. Immune complex disease in either the kidney or skin vessels may be associated with vasculitis and theoretically exacerbated in the presence of filgrastim through recruitment of neutrophils to the deposits of the immune complex. In most cases, filgrastim has been continued at the same or a reduced dose, or after a brief interruption of treatment. Patients with recurrent hematuria associated with glomerulonephritis should be evaluated for immune complex disease and by renal biopsy. It is clear from the survey that there are other potential causes of hematuria including urinary tract infections, autoimmune disease, and malignancy.

Growth and Development

SCN is not known to have a direct relationship to growth and development, although growth may be retarded by chronic infection or inflammation associated with neutropenia, particularly in severe cases. The randomized phase III trial did not demonstrate stimulation or inhibition of growth or development in any group of patients as analyzed from height and weight measurements, Tanner scores, or a variety of endocrine tests. Analysis of weight for height, which is an indirect measure of nutritional status in prepubertal children, shows that the median height for weight percentile remains constant or increases slightly with duration of treatment for all diagnostic groups. Evaluation of growth and development parameters continued with the collection of Registry data. These analyses showed that children with SCN are shorter than normal: 27% to 41% were below the 10th percentile of normal height for age. This difference in height persists with filgrastim treatment and is more significant among patients with congenital neutropenia compared to the cyclic and idiopathic types, thus suggesting a relationship to severity of illness.

Abnormalities in development not attributed to a known medical condition were reported in six patients. Two of these were cases of developmental delay and four of delayed sexual maturation. In summary, with an average of 5 years of follow-up data for 731 patients (59% under 18 years of age), the Registry data do not suggest any adverse effect of filgrastim on either growth or development.

Pregnancy and Fertility

Filgrastim is known to cross the placenta in several species of mammals, including humans.[6-8,16,17] During the filgrastim clinical trials, pregnant patients were either excluded or withdrawn. Despite this protocol exclusion, three did become pregnant while on study and, although all were withdrawn from study, each continued on commercial filgrastim. Two of the patients had cyclic neutropenia: one gave birth to a healthy infant and the second electively aborted one pregnancy and subsequently carried a second pregnancy to term, giving birth to an otherwise healthy child with cyclic neutropenia. The third pregnant patient with idiopathic neutropenia required a therapeutic abortion due to abnormal bleeding, following which she died of a thrombotic event probably related to the pregnancy.

Given the lack of historical information regarding pregnancy outcomes in patients with SCN, the SCNIR requested obstetrical history on all enrolled female patients both at the time of registration as well as with each report of pregnancy. The high percentage (87%) of nontreated cases is indicative of the number of cases obtained from the obstetrical history of Registry patients who conceived prior to the availability of cytokine therapy.

The Registry has collected data on 121 pregnancies among 48 patients. Filgrastim was administered in 16 of these cases for an average of two trimesters (range, one to three) at an average dose of 2.7 μg/kg/d (range, 0.2 to 12.0). Eleven pregnancies continued to a live birth, without congenital abnormalities or newborn complications. Three pregnancies spontaneously aborted and two were electively terminated.

The remaining 105 pregnancies did not involve filgrastim exposure. The outcome was 77 live births, 24 spontaneous abortions (one case of maternal sepsis), and eight induced terminations (nonmedical). Of the 77 live births (including two sets of twins), 72 neonates were healthy and five had major medical complications (primarily respiratory) that required prolonged hospitalization.

No congenital abnormalities were reported in either the filgrastim-treated or the nontreated pregnancies. Data from the Registry indicate that the overall rate of termination among filgrastim-treated women versus women who were not treated with filgrastim is equivalent. However, the rate of both spontaneous abortions and newborn complications requiring hospitalization is slightly higher among women who did not receive filgrastim during pregnancy. Although these differences might reflect a healthier status of the treated mother, the number of pregnancies among filgrastim-treated women is still too small to draw definite conclusions.

In addition to the SCNIR cases, Amgen's clinical safety department has received postmarket reports of pregnancy in nine filgrastim-treated non-Registry SCN patients: four congenital abnormalities (renal and/or cardiac), one spontaneous miscarriage, and four normal neonates.[4] Although these four reports of congenital abnormalities are important, it is of note that similar outcomes have not been found among prospectively collected SCNIR cases.

Registry data indicate that filgrastim used during pregnancy probably does not lead to higher rates of fetal death or congenital anomalies compared to untreated women. Further information is still required to better determine the possible effects on reproductive function and embryogenesis and at present no recommendations can be made regarding the safety of filgrastim during pregnancy.

Leukemic Transformation

The development of cytogenetic abnormalities, MDS, and leukemia has been a major focus of the Registry. In the precytokine era, many congenital neutropenia patients died from infection in the first years of life. Most patients treated with filgrastim do not develop life-threatening infections and survive well beyond 2 years of age. Therefore, it cannot be known whether filgrastim contributes to the development of these conditions or if the increased survival leads to a higher risk for leukemogenesis.

As of December 31, 2000, leukemic transformations have occurred only in patients with congenital neutropenia, who have a crude rate for development of MDS/AML of 9%. Life-table analysis revealed that the cumulative risk of developing leukemia or MDS by the end of the eighth year of filgrastim treatment in a patient with congenital neutropenia was 13% (95% confidence interval, 8.4% to 18%), which represents an annual rate of 1.7%. No apparent trends were found between the leukemic conversion rate with age and duration of filgrastim administration.

Mortality

The Registry has data on 71 SCN patients (57 congenital, 1 cyclic, 13 idiopathic) who died either during clinical trials or while enrolled in the SCNIR. The median age at death was 12 years (range, 0.33 to 89). The leading cause of death remains malignancy or complications related to malignancy for patients with congenital neutropenia, and infection for both cyclic and idiopathic types of neutropenia.

Conclusion

Filgrastim is very effective for the long-term management of SCN. Treatment usually requires daily or alternate-day subcutaneous injections. Long-term treatment is associated with relatively few adverse

events. Bone pain, commonly noted early in treatment, tends to resolve spontaneously. Other blood cell counts usually are not affected. Children on long-term filgrastim treatment have normal growth and development. Mild splenic enlargement is common, but generally asymptomatic and of little clinical consequence. Some cases of congenital neutropenia (9%), but not cyclic or idiopathic neutropenia, evolve into chromosomal abnormalities, MDS, or leukemia. Registry analysis of patients who received filgrastim for up to 11 years (average of 5 years) has not identified any adverse events associated with long duration of treatment.

References

1. Bonilla MA: Clinical efficacy of recombinant human granulocyte colony stimulating factor (r-metHuG-CSF) in patients with severe chronic neutropenia. Blood 133a:524, 1990 (suppl 1, abstr)
2. Bonilla MA, Dale D, Zeidler C, et al: Long-term safety of treatment with recombinant human granulocytic colony-stimulating factor (r-metHuG-CSF) in patients with severe congenital neutropenias. Br J Haematol 88:723-730, 1994
3. Bonilla MA, Gillio AP, Ruggeiro M, et al: Effects of recombinant human granulocyte colony-stimulating factor on neutropenia in patients with congenital agranulocytosis. N Engl J Med 320:1574-1580, 1989
4. Boxer L, Dale D, Bonilla MA, et al: Administration of r-metHuG-CSF during pregnancy in patients with severe chronic neutropenia (SCN). Blood 86:508a, 1995 (suppl 1, abstr)
5. Boxer LA, Hutchinson R, Emerson E: Recombinant human granulocyte-colony-stimulating factor in the treatment of patients with neutropenia. Clin Immunol Immunopathol 62: S39-S46, 1992 (suppl)
6. Calhoun DA, Christensen RD: Assessment of transplacental passage of recombinant human granulocyte colony-stimulating factor in women with an imminent preterm delivery. J Invest Med 44:114a, 1996 (abstr)
7. Calhoun DA, Christensen RD: A randomized pilot trial of administration of granulocyte colony-stimulating factor to women before preterm delivery. Am J Obstet Gynecol 173: 766-771, 1998
8. Calhoun DA, Rosa C, Christensen RD: Transplacental passage of recombinant human granulocyte colony-stimulating factor in women with an imminent preterm delivery. Am J Obstet Gynecol 174:1306-1311, 1996
9. Dale DC: Hematopoietic growth factors for the treatment of severe chronic neutropenia. Concise review. Stem Cells 13: 94-100, 1995
10. Dale DC, Bonilla MA, Davis MW, et al: A randomized controlled phase III trial of recombinant human G-CSF for treatment of severe chronic neutropenia. Blood 81:2496-2502, 1993
11. Donadieu J, Boutard P, Bernatowska E, et al: A European phase II study of recombinant human granulocyte colony-stimulating factor (rHuG-CSF; Lenograstim) in the treatment of severe chronic neutropenia in children. Eur J Pediatr 156: 693-700, 1997
12. Donadieu J, Maeir-Redelsperger M, Fenneteau O, et al: Second neoplasia and mortality in congenital neutropenia: Data from the French severe chronic neutropenia register. Meeting of the American Society of Hematology, San Diego, CA, December 5-9, 1997
13. Hammond WP, Price TH, Souza LM, et al: Treatment of cyclic neutropenia with granulocyte colony-stimulating factor. N Engl J Med 320:1306-1311, 1989
14. Jakubowski AA, Souza L, Kelly F, et al: Effects of human granulocyte colony-stimulating factor in a patient with idiopathic neutropenia. N Engl J Med 320:38-42, 1989
15. Jayabose S, Tugal O, Sandoval C, et al: Recombinant human granulocyte colony-stimulating factor in cyclic neutropenia: Use of a new 3-day-a-week regimen. Am J Pediatr Hematol Oncol 16:338-340, 1994
16. Medlock ES, Kaplan DL, Cecchini M, et al: Granulocyte colony-stimulating factor crosses the placenta and stimulates fetal rat granulopoiesis. Blood 81:916-922, 1993
17. Novales JS, Salva AM, Modanlou HD, et al: Maternal administration of granulocyte colony-stimulating factor improves neonatal rat survival after a lethal group B streptococcal infection. Blood 81:923-927, 1993
18. Rappeport JM, Parkman R, Newburger P, et al: Correction of infantile agranulocytosis (Kostmann's syndrome) by allogeneic bone marrow transplantation. Am J Med 68:605-609, 1980
19. Ryan M, Will AM, Testa N, et al: Severe congenital neutropenia unresponsive to G-CSF. Br J Haematol 91:43-45, 1995
20. Sandoval C, Parganas E, Wang W, et al: Lack of alterations in the cytoplasmic domains of the granulocyte colony-stimulating factor receptors in eight cases of severe congenital neutropenia. Blood 85:852-853, 1995
21. Souza LM, Boone TC, Gabrilove J, et al: Recombinant human granulocyte colony stimulating factor: Effects on normal and leukemic myeloid cells. Science 232:61-64, 1986
22. Welte K, Bonilla MA, Gillio AP, et al: Recombinant human granulocyte colony stimulating factor: Effects on hematopoiesis in normal and cyclophosphamide-treated primates. J Exp Med 165:941-948, 1987
23. Welte K, Boxer L: Severe chronic neutropenia: Pathophysiology. Semin Hematol 34:267-278, 1997
24. Welte K, Dale D: Pathophysiology and treatment of severe chronic neutropenia. Ann Hematol 72:158-165, 1996
25. Welte K, Zeidler C, Reiter A, et al: Differential effects of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor in children with severe congenital neutropenia. Blood 75:1056-1063, 1990
26. Weston B, Todd RF III, Axtell R, et al: Severe congenital neutropenia: Clinical effects and neutrophil function during treatment with granulocyte colony-stimulating factor. J Lab Clin Med 117:282-290, 1991
27. Zeidler C, Welte K, Barak Y, et al: Stem cell transplantation in patients with severe congenital neutropenia without evidence of leukemic transformation. Blood 95:1195-1198, 2000