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Review

MANAGEMENT OF KOSTMANN SYNDROME IN THE G-CSF ERA

Kostmann (1956, 1975) described an inherited haematological disorder with severe neutropenia with an absolute neutrophil count (ANC) $< 0{\cdot}2 \times 10^9$/l and early onset of severe bacterial infections. Most children died because of these infections, despite antibiotic treatment. Different treatment strategies for congenital neutropenia (CN) included use of steroids and lithium (Barrett *et al*, 1977; Hraker *et al*, 1977), but these treatments did not show any long-term effect on neutrophil counts. Bone marrow transplantation (BMT) was the only curative treatment option for patients with human leucocyte antigen (HLA)-compatible donors (Rappeport *et al*, 1980). Some patients who survived infections and treatment, however, underwent malignant transformation into acute myeloid leukaemia (AML) (Gilman *et al*, 1970; Rosen & Kang, 1979).

The availability of recombinant human granulocyte colony-stimulating factor (rHuG-CSF) in 1987 (Nagata *et al*, 1986; Souza *et al*, 1986) dramatically changed both the prognosis of CN and the quality of life for patients with CN (Bonilla *et al*, 1989; Welte *et al*, 1990). Since the establishment of the Severe Chronic Neutropenia International Registry (SCNIR) in 1994, data on 304 patients with CN have been collected to monitor the clinical course, treatment and disease outcomes in these patients. In clinical trials, $>90\%$ of these patients responded to rHuG-CSF treatment with an increase in ANC $> 1{\cdot}0 \times 10^9$/l. Importantly, all responding patients required significantly fewer antibiotics and days of hospitalizations (Dale *et al*, 1993; Bonilla *et al*, 1994; Welte & Dale, 1996; Freedman, 1997; Welte & Boxer, 1997). Haematopoietic stem cell transplantation (HSCT) remains the only currently available treatment for those patients refractory to rHuG-CSF treatment that continue to have severe and life-threatening bacterial infections. Data from the SCNIR also demonstrate that for all CN patients, $\approx 9\%$ will develop leukaemia regardless of their treatment or response (Bonilla *et al*, 1994; Freedman, 1997; Welte & Boxer, 1997). The molecular and genetic basis for this disease is still largely unknown.

DIAGNOSIS

Kostmann (1956) originally described a Swedish kindred with severe congenital neutropenia inherited as an autosomal recessive trait without additional haematological changes or other congenital abnormalities. This diagnosis is now often used for similar cases without a defined pattern of inheritance. We therefore prefer the term congenital neutropenia (CN) for the description of this patient population. The estimated frequency of this disorder is $\approx 1-2$ cases per million with equal distribution for gender.

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Onset of symptoms

In patients with CN, severe bacterial infections frequently occur during the first year of life. Omphalitis beginning directly after birth may be the first symptom, but also otitis media, pneumonitis and infections of the upper respiratory tract, abscesses of skin or liver are common infections which often lead to diagnosis. Cultures are mainly positive for *Staphylococci* or *Streptococci*, but also other bacteria, for example *Pseudomonas* and *Peptostreptococcus*, and fungi have been detected.

Blood values

For diagnosis, repeated differential blood counts are required, indicating persistent ANC within a range of 0–$0{\cdot}2 \times 10^9$/l. Blood counts often also indicate mild anaemia and thrombocytosis. There may also be increases in blood monocytes and eosinophils. Immunoglobulin levels for IgG are elevated in the majority of patients independent of their infectious status (unpublished data). The specific immunological competence after vaccination is also normal. Blood chemistry is within the normal age-dependent range for electrolytes, kidney and liver function.

Bone marrow

The bone marrow usually shows a maturation arrest of neutrophil precursors at an early stage (promyelocyte–myelocyte level) with few cells of the neutrophilic series beyond the promyelocyte stage. The number of promyelocytes is slightly increased (Welte & Boxer, 1997). Marrow eosinophilia is common. Cellularity is usually normal or slightly decreased. Megakaryocytes are normal in number and morphology. The *in vitro* growth of granulocyte colonies in granulocyte–macrophage colony-forming unit (GM-CFU) assays is often defective with a maturation arrest that mimics the disease.

Pathophysiology

The underlying genetic defect of Kostmann syndrome has still not been identified. In another congenital disorder associated with severe neutropenia, the glycogen-storage disease type 1b, the gene responsible for the disease maps to human chromosome 11q23 (Annabi *et al*, 1998).

The original hypothesis for Kostmann syndrome included

Table I. Differential diagnosis of Kostmann syndrome.

Other congenital neutropenias
Cyclic neutropenia
Myelokathexis
Chédiak–Higashi syndrome
Inborn errors of metabolism
Shwachman–Diamond syndrome (SDS)
Pearson syndrome
Glycogen-storage disease type Ib (GSD Ib)
Methylmalonic aciduria (MMA)
Immunodeficiencies
Hyper IgM syndrome
Agammaglobulinaemia
Large granular lymphocyte syndrome (LGL)
Severe combined immunodeficiency (SCID)
Immune neutropenia
Autoimmune neutropenia
Alloimmune neutropenia
Idiopathic neutropenia

a genetic predisposition resulting in defective production of G-CSF or defective response of the neutrophilic precursors to G-CSF or other haematopoietic growth factors. Western blot analysis and *in vitro* bioassays have shown that serum from patients with Kostmann syndrome contain normal or increased levels of G-CSF (Mempel *et al*, 1991) with normal biological activity of endogenous G-CSF.

G-CSF receptors are expressed on myeloid cells from patients with Kostmann syndrome (Kyas *et al*, 1992). The numbers of G-CSF receptors are slightly increased. The binding constant for G-CSF to its receptor is normal. In CN patients who have developed leukaemia, acquired G-CSF receptor mutations affecting the cytoplasmic domain were present in most patients tested so far (Dong *et al*, 1995; Tidow *et al*, 1997; Bernard *et al*, 1998; Germeshausen *et al*, 1999), suggestive of an important role of these mutations in the leukaemogenesis. The G-CSF receptor mutations so far have never been detectable from birth, indicating that these mutations are not responsible for the neutropenia but have developed through the course of life in a small subgroup of patients and are most likely caused by genetic instability. Therefore, G-CSF receptor analysis cannot be used for diagnostic purposes for the underlying disease, but might be helpful in screening for the risk of leukaemia.

Differential diagnosis

Differential diagnosis of Kostmann syndrome includes a number of other congenital or inherited disorders as well as the acquired diseases listed in Table I.

The most common of these rare diseases (cyclic neutropenia, Shwachman–Diamond syndrome, glycogen-storage disease type 1b and autoimmune neutropenia in infancy) are described in more detail (see also Fig 1).

Cyclic neutropenia.. If infections (typically aphthous stomatitis) occur frequently at ≈ 3-week intervals, cyclic neutropenia should be considered and serial differential

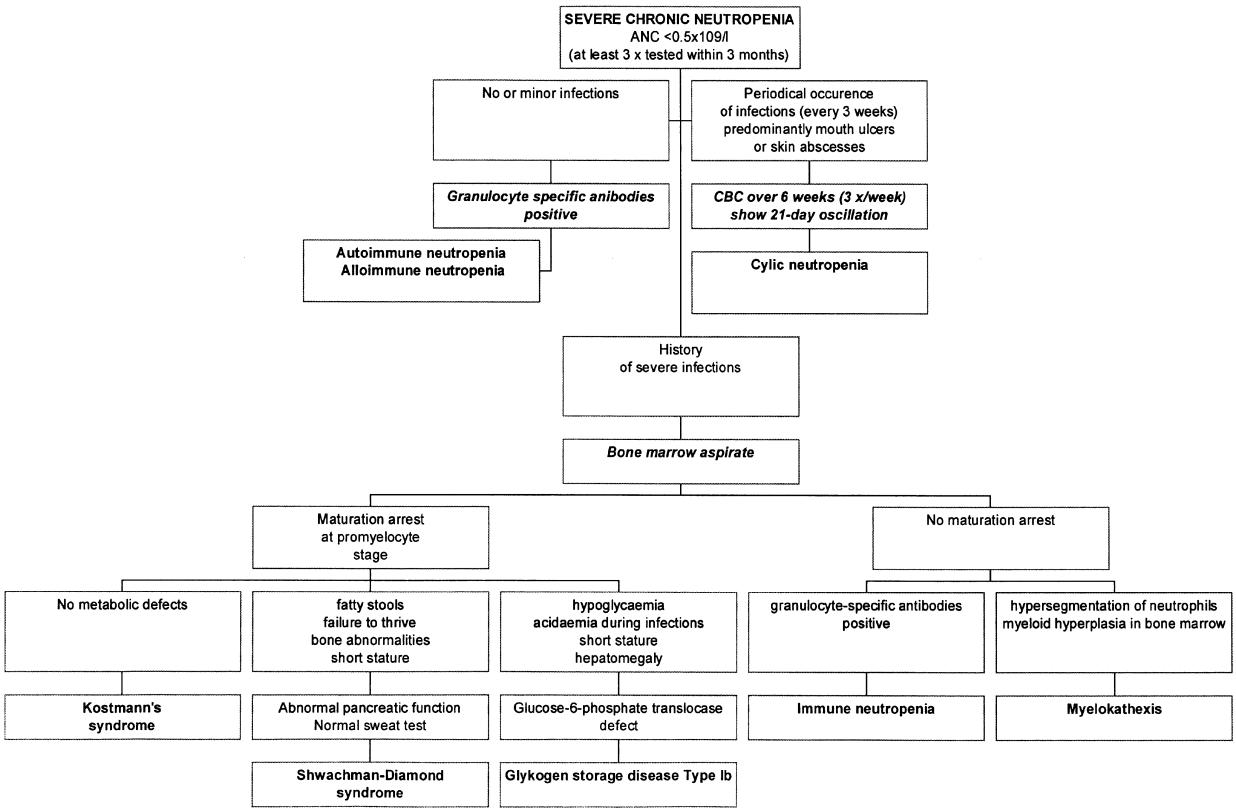

Fig. 1. Diagnostic procedure in neutropenia.

blood counts should be performed (at least three times per week over 6 weeks) to search for the typical cyclical pattern of blood neutrophils. Almost all patients with clinically obvious cyclic neutropenia have periods of severe neutropenia (ANC $< 0{\cdot}2 \times 10^9$/l) every 3 weeks showing some symptoms with almost every cycle, but significant infections (for example otitis, pneumonia and bacteraemia) usually are infrequent. Cyclic neutropenia occurs because of fluctuating rates of cell production by the bone marrow (Quesenberry, 1983; Dale & Hammond, 1988). In contrast to other causes of neutropenia, in this disease the marrow oscillates between normal appearance and that of severe 'maturation arrest' of neutrophilic series. Other blood cells, such as platelets or reticulocytes, typically also show oscillations with a cyclical pattern. Cyclic neutropenia can occur sporadically, but there are families in which cyclic neutropenia is inherited in an autosomal dominant pattern (Morley et al, 1967). As in Kostmann syndrome, patients with cyclic neutropenia also benefit from rHuG-CSF treatment (Hammond et al, 1989).

Other forms of rare neutropenia (Shwachman–Diamond syndrome and glycogen-storage disease type 1b.. Patients who present with fatty and voluminous stools need testing for pancreatic function to rule out Shwachman–Diamond syndrome (SDS), which is an autosomal recessive disorder with multisystemic abnormalities, including exocrine pancreatic insufficiency, neutropenia and short stature. At the time of diagnosis, the phenotype of SDS is extremely variable. The vast majority of patients are diagnosed in infancy, with symptoms of steatorrhoea and poor growth, with or without haematological abnormalities (Smith et al, 1996), but other less common manifestations can also be evident at diagnosis. These include extreme short stature, skeletal abnormalities, and marked hepatomegaly (Aggett et al, 1980; Ginzberg et al, 1999).

Glycogen-storage disease type 1b is a rare metabolic disorder which affects the transport system of glucose-6-phosphatase metabolism. Patients present with hepatomegaly, failure to thrive, renal dysfunction and recurrent infections. Chronic neutropenia in these patients is accompanied by phagocytic cell dysfunction, including decreased superoxide anion (O_2^-) generation, calcium (Ca^{2+}) mobilization and chemotactic activity. Patients responded to treatment with r-metHuG-CSF, not only with an increase in ANC but also with improvement of the phagocytic activity of their neutrophils (Schroten *et al*, 1991; McCawley *et al*, 1994).

Presence of neutrophil specific antibodies.. In children aged 1–3 years with neutropenia not caused by Kostmann syndrome, presence of neutrophil-specific autoantibodies can result in increased peripheral destruction of neutrophils. Although these infants lack peripheral blood neutrophils, they usually do not suffer from severe bacterial infections. In the serum of these patients, granulocyte-specific antibodies are detectable by different immunological tests (Bux et al, 1998).

TREATMENT

Since 1987, rHuG-CSF has been available for treatment of CN. Phase I–III studies demonstrated the efficiency of rHuG-CSF on increasing the number of neutrophils that is associated with reduction of infections (Bonilla *et al*, 1989; Dale *et al*, 1993). In contrast, granulocyte–macrophage colony stimulating factor (GM-CSF) treatment does not lead to an increase in blood neutrophils, but only blood eosinophils (Welte *et al*, 1990).

In 1994, the Severe Chronic Neutropenia International Registry (SCNIR) was established in order to collect data on clinical course and outcome of these rare disorders. As of 31 December 1998, 304 patients with CN have been registered with the SCNIR. Of these 304 patients, $> 95\%$ responded to rHuG-CSF treatment, with an increase in absolute neutrophil counts of $\geq 1{\cdot}0 \times 10^9$/l. Most CN patients respond to doses between 3 and 10 μg/kg/d.

Dosing of rHuG-CSF is described in Table II and Fig 2. After initiation of rHuG-CSF with 5 μg/kg/d, the dose should be escalated to 10 μg/kg/d and then by increments of 10 μg/kg at 14-d intervals if the ANC remains below $1{\cdot}0 \times 10^9$/l. As soon as the ANC can be maintained at

Table II. RHuG-CSF dosing in patients with severe chronic neutropenia.

Diagnosis	*n*	Mean (μg/kg/d)	Median (μg/kg/d)	Range (μg/kg/d)
Congenital	241	12·8	6·0	0·3–240
Cyclic	101	2·5	2·2	0·5–11
Idiopathic	153	2·4	1·1	0·3–55

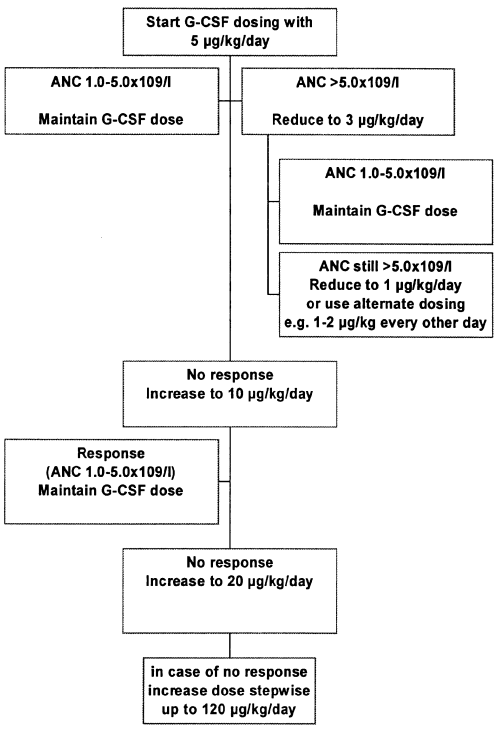

Fig. 2. Dosing of G-CSF in congenital neutropenia patients.

$\geq 1{\cdot}0 \times 10^9$/l, the rHuG-CSF dose does not need to be increased further as the occurrence of bacterial infection can be reduced dramatically with an ANC at this level. rHuG-CSF dose can be reduced if the ANC increases to $5{\cdot}0 \times 10^9$/l or above to maintain the patient at the lowest dose necessary for maintaining a sufficient neutrophil count to overcome infections. Non-responders to rHuG-CSF are defined as those patients failing to respond to rHuG-CSF levels exceeding 120 μg/kg/d. Partial responders can increase their ANC to $0{\cdot}5$–$1{\cdot}0 \times 10^9$/l, but still have bacterial infections. In these patients, the dose of rHuG-CSF could not be increased because of the large volume and frequency of injections required. In some of these patients, a combination of rHuG-CSF with stem cell factor (SCF) led to an further increase in ANC. Because of potential allergic side-effects from SCF, this treatment combination has been only used during severe infections in hospitalized patients who receive concomitant antihistamine medication (Zeidler *et al*, 1998). For those patients who do not respond to rHuG-CSF treatment alone or in combination with SCF, HSCT is the only currently available treatment (Zeidler *et al*, 2000). When successful, patients achieve normal haematopoiesis after transplantation and do not require cytokine treatment. It remains difficult to give a recommendation for transplantation for patients with CN who benefit from rHuG-CSF and who show no evidence of impending malignant transformation. The risks associated with transplant from an HLA-identical sibling may outweigh the risk of leukaemic transformation when rHuG-CSF is continued in responding patients. If the risks of HSCT could be decreased by using a low-intensity regimen and inducing tolerance by mixed chimerism, then HSCT from a matched sibling donor may be used in the future.

LONG-TERM SAFETY

Leukaemia

Before the availability of cytokine therapy, it had been recognized that leukaemic transformation occurred in patients with congenital neutropenia (Gilman *et al*, 1970; Rosen & Kang, 1979). However, in the precytokine era, 42% of published cases died in the first 2 years of life, usually from sepsis or pneumonia. Thus, the true risk of congenital neutropenia patients developing myelodysplastic syndrome (MDS)/AML was not defined. With rHuG-CSF therapy, most of these patients have survived well beyond 2 years of age. Therefore, it is unknown whether the increased survival allows for a higher risk of the recognized natural expression of leukaemogenesis in this population in the absence of rHuG-CSF therapy.

From the initiation of clinical trials with rHuG-CSF in 1987 until December 1998, a total of 31 severe CN (SCN) patients who had developed MDS/AML were reported to the SCNIR, all of whom have a diagnosis of congenital neutropenia. The overall incidence or crude rate of MDS/AML conversion was 8·8% for CN patients (31 cases among 352 exposed cases), with an average follow-up of approximately 5–6 years. Two of the total 31 congenital patients were diagnosed as having Shwachman–Diamond syndrome. No cases of MDS/AML occurred in the subgroup of patients suffering from cyclic or idiopathic neutropenia.

Conversion to MDS/AML in SCN patients was associated with one or more cellular genetic abnormalities, for example monosomy 7, *ras* mutation or G-CSF receptor mutation, which may be useful to identify subgroups of patients at high risk (Dong *et al*, 1995; Tidow *et al*, 1997). Of 31 patients who transformed in the registry series, 18 developed partial or complete loss of chromosome 7 (7q– or monosomy 7) in marrow cells.

Interestingly, marrow cells from 11 SCN patients who transformed to MDS/AML also showed point mutations in the gene for G-CSF receptor, resulting in a truncated C-terminal cytoplasmic region of the receptor that is crucial for maturation signalling (Dong *et al*, 1995; Tidow *et al*, 1997; Germeshausen *et al*, 1999).

As illustrated by the cases described herein, the development of MDS/AML is a multistep process characterized by a series of cellular genetic changes, indicating a genetic predisposition to malignant transformation. If and how rHuG-CSF might have an impact upon this predisposition remains unclear; there are no historical controls for comparison to resolve this. To address further the issue of risk benefit of rHuG-CSF in the SCN setting with regard to MDS/AML, all available data were critically reviewed (Freedman, 1997). It was recommended by the SCNIR advisory board that annual marrow cytogenetic testing to identify monosomy 7 or other changes indicating transformation is highly recommended in patients with congenital neutropenia. This will allow early therapeutic intervention such as bone marrow transplantation.

Osteoporosis

The initial observation of bone pain and pathological fractures in a number of our patients led us to investigate bone mineral density in a cohort of 30 patients (Yakisan *et al*, 1997); of these 30 patients, 15 (50%) had evidence of osteopenia/osteoporosis and in 5 of the 15 patients osteoporosis became a clinical problem with either pathological fractures or moderate back pain.

Within the SCNIR, bone density measurements have been reported on a total of 121 patients with CN measured by different techniques, including quantitative computerized tomography (Q-CT), dual energy X-ray absorptiometry (DEXA), single photon absorptiometry (SPA) and lumbar radiograph. Within these 121 patients, 66 (54·4%) had varying degrees of abnormal results. These results have not been quantified to interpret severity of abnormality. Most patients did not show clinical symptoms of osteopenia/osteoporosis such as bone pain or fractures, which helps to explain the reason why diagnostic procedures for bone density evaluation have not been reported in $\approx$ 70% of registry patients. Therefore, the actual incidence continues to remain unknown. The pathophysiology of osteopenia/osteoporosis also remains unclear. Serum chemistry did not reveal a typical pattern in patients with osteopenia/osteoporosis. Patients also did not receive elevated amounts of rHuG-CSF doses compared with all registry patients.

Vasculitis

Vasculitis has been reported in 3·3% (9/270) of patients with CN. Symptoms of vasculitis generally developed simultaneously with an increase in ANC and abated when ANC decreased. The results of the survey indicated that patients with recurrent vasculitis, or with renal involvement, need to be evaluated for other diseases. Vasculitis may be associated with autoimmune disorders or an underlying malignancy. After a temporary disruption of rHuG-CSF administration, the vasculitis has abated in all patients.

Splenomegaly

In patients with congenital neutropenia, the incidence of palpable splenomegaly (2 cm below the costal margin) before treatment with rHuG-CSF was 20·6%. During the first year of rHuG-CSF therapy, the incidence increased to 38·9% and remained approximately at this level of occurrence (33·8–47·6%) over 10 years of therapy. Allowing for rHuG-CSF dose, there seems to be a general increase in spleen size with time. In some individuals, splenomegaly is associated with infections or with transformation to MDS/AML.

MONITORING

All patients should be seen by a physician at least twice per year. Blood counts (whole blood count, haemoglobin, platelets and differential blood counts) and physical examination should be obtained at least every 3 months, including assessment for weight and height and documentation of intercurrent infections.

Bone marrow examination (morphology plus cytogenetics) is required once per year to search for acquired cytogenetic abnormalities, such as monosomy 7 or trisomy 21. Additionally, after informed consent, bone marrow samples will be collected from CN patients for a variety of research studies for molecular analysis of the pathophysiology of CN.

Additionally, G-CSF receptor analysis is performed on heparinized blood or bone marrow samples by laboratories headed by the SCNIR.

CONCLUSIONS

In light of the reported studies and longitudinal data from the SCNIR, we suggest that the use of rHuG-CSF remains as the first-line treatment for most CN patients.

Human stem cell transplantation (HSCT) from an HLA-identical sibling is beneficial for CN patients refractory to rHuG-CSF. For those patients in whom a G-CSF receptor mutation is identified, HSCT from an HLA-identical sibling is an option. Patients who develop monosomy 7, other significant chromosomal abnormalities or MDS/leukaemia should proceed urgently to HSCT. Data on alternative sources of donor stem cells are insufficient to assess outcome in patients with CN. Other than those patients who fail to respond to rHuG-CSF, the cytokine should be used to maintain an ANC ranging from 1·0 to 5·0 $\times$ 10^9/l with amelioration of symptoms.

All CN patients, regardless of their treatment or response, have a 9% risk of developing MDS or leukaemia. Careful monitoring for cytogenetic abnormalities and G-CSF receptor mutation is necessary to initiate HSCT as soon as any of these occur. Despite the significant risk of leukaemia, HSCT-related morbidity is also significant and therefore without signs of leukaemia or a preleukaemic state HSCT should be restricted to G-CSF non-responders.

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