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Hematopoietic Stem Cell Transplantation for Severe Congenital Neutropenia

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Abstract

Purpose of review—Hematopoietic stem cell transplant (HCT) is the only curative option for patients with severe congenital neutropenia (SCN). Transplant success is dependent on identifying at risk patients and proceeding to transplant before the development of severe infections or malignant transformation. This review focuses on recent advancements in risk stratification of SCN patients, indications for HCT, and review of published transplant studies.

Recent findings—Patients with poor neutrophil response despite high doses of granulocyte colony-stimulating factor (G-CSF) are at greatest risk for malignant transformation. Other studies demonstrate elevated risk with mutations in the G-CSF receptor gene and a specific mutation in the ELANE gene. These patients are at high-risk of sepsis or leukemia development and should proceed to transplant with best available donor. As recent published studies demonstrate, HCT is highly successful in patients without leukemia and therefore may be considered in selected low-risk patients given the life-long risk of malignancy and infection.

Summary—The decision whether to proceed to HCT in healthy patients maintained on G-CSF is difficult. As transplant related mortality continues to decrease, the role of transplant in severe congenital neutropenia is likely to expand to more patients.

Keywords

severe congenital neutropenia; hematopoietic stem cell transplant; G-CSF; leukemia

Introduction

Severe Congenital Neutropenia (SCN) is a diverse group of rare disorders that is characterized by severe neutropenia with a peripheral blood absolute neutrophil count (ANC) of less than 500, maturation arrest of myeloid precursors at the promyelocyte/myelocyte stage within the bone marrow[1, 2], and recurrent bacterial infections[3]. The estimated frequency is 1–2 cases per million[4] with a slight male predominance[5]. Autosomal dominant, X-linked, and sporadic forms are referred collectively as SCN while the term Kostmann's Disease (after Rolf Kostmann who first described the disorder in 1956[6]) is reserved for autosomal recessive inheritance. Before the introduction of modern therapies, SCN was highly fatal with 50% mortality in the first year of life from bacterial sepsis and a subsequent mortality rate during the second through fourth years of 6 to 7% per

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year[7]. In addition, for patients who survived infection, it was identified that SCN also predisposes patients to the development of myelodysplastic syndrome (MDS) and leukemia. The most common leukemia in SCN is acute myeloid leukemia (AML), but acute lymphoid leukemia (ALL), juvenile myelomonocytic leukemia (JMML)[8], chronic myelomonocytic leukemia (CMML)[9], and bi-phenotypic leukemia are also reported in the literature.

Pathophysiology and Genetics

Since the original description by Kostmann, a number of genetic mutations has been identified that likely cause or contribute to SCN. The most common mutation is found in the serine protease neutrophil elastase (NE) transcribed by the gene ELANE (previously known as ELA2) and is found in 50–60% of patients with SCN [10, 11]. NE is initially produced at the promyelocyte stage and later packaged within primary granules in mature neutrophils [12, 13]. Over 50 mutations of ELANE have been identified and all mutations are inherited in an autosomal dominant fashion. Mutations in ELANE result in a misfolded NE protein which induces the unfolded protein response leading to apoptosis of the myeloid precursor [14, 15].

Mutations in the HAX1 gene are a cause of autosomal-recessive SCN. HAX1 is a ubiquitously-expressed mitochondrial protein and a homozygous defect results in loss of mitochondrial membrane potential and release of pro-apoptotic proteins that lead to programmed cell death[16, 17]. Mutations that affect both transcript variants of HAX1 also present with developmental delay and epilepsy[18]. Initial analysis of mutation frequency identified HAX1 mutations in 30% of patients with SCN [17]. However, in a recent investigation of North American SCN samples, no HAX1 gene mutations were detected in 162 patients indicating that it may be a less frequent cause[19]. Mutations in Wiskott-Aldrich syndrome protein (X-linked recessive), growth factor-independent protein 1 (GFI1; autosomal dominant), granulocyte colony-stimulating factor receptor (G-CSFR; autosomal dominant), and glucose-6-phosphatase, catalytic subunit 3 (G6PC3; autosomal recessive) are uncommon genetic variants of SCN. A significant number of cases including 40% of the North American samples have a yet undefined molecular defect [19].

Although SCN patients with heterogeneous mutations will present with similar bone marrow findings and predisposition to infection, differences in treatment and clinical outcome have been detected in patient cohorts. Different groups have evaluated the clinical consequence of ELANE mutations, but the significance of wild type (WT) versus a mutated gene is unclear. A North American analysis found that ELANE mutations correlate with better outcomes [10] while European studies showed the opposite with increased need for G-CSF and more infections [12]. A common finding in both studies was the correlation of the Gly185Arg mutation in ELANE and a very severe clinical course requiring high doses of G-CSF and high-risk of leukemia transformation.

CSF3R Mutations

Mutations in the CSF3R gene which encodes the G-CSF-R are common in patients with SCN (7–40%) and were originally believed to be the etiology of this disease [20–22]. Although there are a few cases of constitutive mutations in the extracellular component of the G-CSF-R that cause SCN through a hyporesponsive response to G-CSF (G-CSFR^{hypo}) [23], the majority of defects are somatic mutations acquired during the course of the illness. The acquired mutation in almost all cases is a nonsense mutation that results in loss of the c-terminal fragment critical for transducing maturation signals and suppressing cell proliferative signals[20, 24]. The proximal cytoplasmic region that transduces proliferative and survival signals is preserved. Cells containing this mutation have increased STAT5 phosphorylation[18] which may lead to downregulation of myeloid-associated

differentiation factors such as C/EBP α [25] and LEF-1 [26]. Myeloid cell lines with expression of mutated G-CSF-R have enhanced proliferation [27], resistance to apoptosis, and increased cell survival [28]. Knock-in mice revealed hyperproliferative responsiveness to exogenous G-CSF [29] and a strong clonal advantage to affected cells [30], leading to the nomenclature of G-CSF^{hyper} to differentiate from mutations in the extracellular component of the protein.

Despite these experimental findings, patients with G-CSF^{hyper} mutations do not have increased response to G-CSF administration [18]. However, in SCN bone marrow cells harboring the G-CSF^{hyper} mutation, levels of phosphorylated STAT5 [30, 31] and reactive oxygen species production [32] are increased with G-CSF administration. As both of these downstream effects can be a risk for leukemogenesis, it would be expected that patients with G-CSF^{hyper} mutations are at increased risk of leukemia transformation. Germeshausen evaluated 148 patients with SCN and found the prevalence of CSF3R mutations in 78% of patients with monosomy 7, MDS, or leukemia as compared to only 34% of patients without any signs of malignant transformation [20]. Furthermore, in most patients with leukemia, the proportion of mutated mRNA was greater than 50% indicating that all cancer cells harbored a heterozygous mutation. However, Germeshausen argued that the presence of G-CSFR mutations was unlikely sufficient to cause leukemia as the mutation does not definitively lead to leukemia in a defined time period and leukemia occurred in SCN patients without this mutation. Given the increased risk of transformation once detected, the authors recommended annual mutational screening of CSF3R and consideration of HCT if a mutation was detected. This recommendation has not been universally adopted among physicians caring for SCN patients.

Treatment

Before the era of G-CSF therapy, the majority of patients succumbed to death by bacterial sepsis early in life. In 1987, G-CSF was first used in a SCN child and is now considered frontline therapy for all SCN patients [33]. Analysis of patients on the Severe Chronic Neutropenia International Registry (SCNIR) has demonstrated a significant reduction in the risk of death by sepsis from 50% during the first year of life to a cumulative incidence of 8% at 10 years on G-CSF therapy [7]. Given the genetic heterogeneity of SCN, it is not surprising that response to G-CSF is variable among patients. A minority (10%) of patients fail to achieve an increase in neutrophil count above 1.0×10^9 cells/L despite high doses of G-CSF (≥ 120 $\mu\text{g/kg/d}$) [16].

As most patients with SCN are now escaping death from sepsis, physicians are now realizing an increasing risk of malignant transformation in patients reaching an older age on long-term G-CSF therapy. The most recent evaluation of the SCNIR reported a cumulative incidence of MDS/leukemia at 15 years of 22% [34, 35]. In addition, Rosenberg was able to separate patients into “high” and “low” risk of malignant transformation groups based on their response to G-CSF. Patients who had a robust response to G-CSF, defined as doses below the median dose of 8 $\mu\text{g/kg/day}$ and neutrophil levels above the median of 2.188×10^9 cells/L, had a cumulative incidence after 15 years on G-CSF of 5% for sepsis death and 15% for MDS/leukemia. In contrast, a subset of patients with poor response to G-CSF despite high G-CSF doses had significantly increased risk of mortality with a cumulative incidence of sepsis death of 18% and MDS/leukemia of 34% at 15 years. Rosenberg recommended that patients in this high-risk group be strongly considered for HCT. But the risk of malignant transformation by the teenage years even in the low-risk group is substantial. We have recommended that HCT at least be considered in this population, particularly in patients who have a matched sibling donor [35].

Concerns over G-CSF Treatment

A causative role of G-CSF has not been identified in leukemia development. However, concern continues among investigators that prolonged G-CSF therapy and malignant transformation may be more than just correlation. The increased risk of MDS/leukemia observed by Rosenberg in patients poorly responsive to high doses of G-CSF was also noted in the French Severe Chronic Neutropenia Registry (SCNR)[36]. In addition, the knock-in mouse model of G-CSFR demonstrated a clonal advantage of cells harboring the mutation that was dependent on G-CSF administration[30]. Anecdotal cases have been reported in the literature describing an association with leukemia blast counts and G-CSF administration [9, 37, 38]. These observations have led to the hypothesis that patients with SCN have genotoxic stress secondary to increased pressure for cell division and therefore are at increased risk for mutation. These cells normally handle mutations through cellular senescence, but the hyperproliferative signal provided by G-CSF may bypass senescence signaling and allow malignant clones to develop[18, 39].

However, there are reassuring findings that G-CSF does not play a causative role in leukemia development. The knock-in G-CSFR mutated mice do not develop leukemia despite G-CSF administration [29], although this may be a function of the limited lifespan of mice and underexposure. G-CSFR mutations do not occur in other conditions requiring extensive exposure to G-CSF including Cyclic Neutropenia, Schwachman-Diamond Syndrome and autoimmune neutropenia [20], arguing against G-CSF being a sufficient requirement for mutations to develop. In his most recent analysis, Rosenberg identified the rate of MDS/leukemia to be similar to the rate of AML in other marrow failure syndromes such as Fanconi's Anemia and Dyskeratosis Congenita, conditions that do not rely on prolonged G-CSF administration[34²²]. Unlike earlier reports of increasing risk of MDS/leukemia with each year of G-CSF exposure, this risk appears to plateau and therefore a cumulative lifetime dose of G-CSF leading to high-risk is unlikely to exist.

Indications for HCT

Whether the increased risk of malignant transformation is related to G-CSF therapy or more likely, merely a function of increased escape from early sepsis death, the continuing concern of leukemia risk has raised questions whether long term therapy may not be the best option for all SCN patients. HCT remains the only curative therapy for SCN. The absolute indications for HCT in SCN are a failure to respond to G-CSF or the development of MDS/leukemia. As additional understanding of this disease is gained, further indications for transplant have arisen to prevent high-risk patients from malignant transformation or death from sepsis. High-risk patients that should strongly be considered for HCT include patients who require high doses of G-CSF ($> 8 \mu\text{g/kg/d}$) with poor response in neutrophil counts. There are conflicting results on WT versus mutated ELANE genes, but patients who harbor the Gly185Arg mutation in the ELANE gene should also be strongly considered for HCT with the best available donor.

As suggested by Choi[35], patients who do not meet these criteria should also be considered for transplant if an available matched sibling is identified given their continued risk of death from sepsis and leukemia. In low-risk patients (defined by adequate neutrophil response to low doses of G-CSF and lack of high risk mutations) without a sibling match, the potential acute toxicity from alternative donor transplants generally outweighs the long-term risk of death in these patients. Alternative donor transplants are becoming more common in non-malignant conditions as improvements in donor selection, GVHD prevention, and supportive care have made HCT a safer option. However, alternative donor transplant is not yet recommended for low-risk SCN populations.

Scope of HCT

There are currently 18 published reports of HCT in patients with SCN for a total of 65 patients transplanted without malignant transformation (Tables 1 and 2)[8², 40, 41², 42², 43–51, 52², 53, 54] and 18 patients transplanted with development of MDS or leukemia (Table 3)[8², 41², 43, 55, 56]. Indications for proceeding to transplant have included poor response to G-CSF (most common), development of G-CSFR mutation(s), inability to tolerate G-CSF injections, infection unresponsive to G-CSF and anti-microbials, development of cytogenetic changes consistent with MDS, and morphologic evidence of MDS or leukemia. The combined overall and event free survival (EFS) for patients transplanted without malignant transformation is excellent at 89 and 75% respectively. As expected, HCT outcomes for patients with malignant transformation are inferior.

Donor Source in SCN without Malignant Transformation

The approach to transplant in SCN has been heterogeneous in regards to donor source, conditioning regimen, and supportive care. A matched related donor (MRD) transplant has provided the best chance of transplant success in larger cohorts. Oshima reported survival in 8/9 and EFS in 7/9 patients with 2 patients developing engraftment failure, 1 patient developing acute GVHD and 2 patients with chronic GVHD[42²]. Zeidler reported similar success with survival in 8/8 patients transplanted using a MRD and EFS in 7/8 patients with engraftment failure in 1 patient, acute GVHD in 2 patients, and chronic GVHD in 1 patient[40].

Most patients considered for a HCT will unfortunately not have an available MRD. The majority of unrelated transplants in the literature report umbilical cord(s) as the donor source. The largest published series is from Bizzetto who reported survival in 11/13 patients [8²]. Most of the literature on the use of cords is in single case reports or small series, lending itself to publication bias. With this in mind, the reported combined success is excellent with a survival of 93%. However, the engraftment failure rate is very high at 24%, leading to an EFS of only 76%.

Other donor sources include matched unrelated donors with good survival (7/8 patients) reported but possibly an increased risk of GVHD. Only 3 patients for both mismatched related donors (MMRD) and mismatched unrelated donors (MMUD) have been published.

Conditioning Therapy in SCN without Malignant Transformation

Both myeloablative (MA) and reduced intensity conditioning (RIC) regimens have been used in transplanting SCN patients with institutional preference guiding the choice. The most common MA therapy used has been Busulfan and Cytosan (Bu-Cy) ± anti-thymocyte globulin (ATG), but several other regimens have been employed. RIC therapies in SCN have uniformly included fludarabine in combination with other agents, including low dose irradiation. Survival outcomes following MA conditioning are similar to RIC (92 vs. 87%).

Other non-malignant conditions including Severe Combined Immunodeficiency (SCID) and hemoglobinopathies have explored the option of immune tolerance by allowing persistent mixed chimerism but avoiding graft rejection or significant GVHD. If immune tolerance is achieved in SCN, both donor and recipient myelopoiesis can occur, but only the donor progenitor cells will mature to neutrophils and eliminate the risk of sepsis death. Zeidler examined chimerism in 5 patients who received a MA transplant and identified mixed chimerism in 2 patients[40]. Both had normal counts, remained free from infection, and did not develop leukemia. It is uncertain, however, if remaining recipient progenitor cells still place the patient at risk of MDS/leukemia. If mixed chimerism is found to be tolerated in

SCN transplant recipients, patients potentially could receive less toxic conditioning regimens. At our center, we use fludarabine combined with myeloablative dosing of busulfan (FluBu4) $\pm$ ATG. The addition of ATG provides enhanced T-cell suppression in patients who have not received prior immuno- or myelosuppressive therapy or are receiving alternative donor HCT and therefore are at increased risk of rejection. This regimen has the advantage of low rates of significant toxicity while resulting in reliable full donor chimerism.

HCT in SCN with MDS/Leukemia

Transplant in SCN patients who develop malignant transformation presents a difficult challenge to physicians. Choi reported on 6 patients with MDS or leukemia [55]. All four patients with AML died and had significant toxicity from induction therapy prior to transplant. Two patients with MDS survived. Cumulative survival rates of all published patients reveal estimated EFS of 57% for MDS and 27% for leukemia. These numbers do not reflect unpublished SCNIR data referenced in Zeidler's paper of only 3/18 patients with leukemia who were transplanted before 2000 surviving a HCT[40]. Given the poor outcome of transplant in patients who progress to MDS or leukemia, the onus is to identify these patients early before they progress to dysplasia or malignancy and proceed to transplant with the best available donor. For patients who develop leukemia, minimizing the complications of induction chemotherapy is vital. Our recommendation is to use the least toxic regimen that provides enough cytoreduction to safely get the patient to a HCT. G-CSF is required in these patients to overcome severe neutropenia encountered with induction chemotherapy and minimize infectious complications.

Infectious and GVHD Prophylaxis for Patients Receiving HCT

Patients with chronic neutropenia who proceed to transplant are at high-risk of developing infections. At our center, prophylactic broad spectrum antibiotics and antifungals with mold coverage is started with conditioning therapy. Herpes simplex virus (HSV) and Varicella Zoster virus (VZV) reactivation can be mitigated with acyclovir prophylaxis in susceptible patient populations. Monitoring for cytomegalovirus (CMV) reactivation in seropositive patients and early detection of other herpes viruses such as Epstein Barr Virus (EBV) and Human Herpes Virus-6 (HHV6) in patients receiving directed anti-T cell therapy is necessary. By adopting this approach, our patients have experienced few infectious complications during HCT. GVHD prophylaxis, although not standardized, should be prescribed for an extended course in SCN patients without malignant transformation as they do not benefit from the graft-versus-leukemia effect.

Summary

HCT in patients with SCN takes many different forms but in the majority of patients represents a successful cure of their neutropenia. Absolute indications for HCT exist in the form of G-CSF non-responsiveness and development of MDS/leukemia. However, additional high-risk groups have been identified that place them at risk of sepsis death and malignant transformation. These patients include those who require high doses of G-CSF with only partial response, have a detectable clone harboring a mutation associated with MDS, or have the constitutional Gly185Arg ELANE mutation. High-risk patients should be considered for transplant with the best available donor. As HCT is curative, improvements in transplant related complications should ultimately lead to increased use of this option, even in lower risk patients with alternative donors. Understanding whether post-transplant mixed chimerism increases the risk for later malignant transformation will help physicians determine the intensity of conditioning needed and the necessity of post-transplant immune manipulations. Finally, as research continues to provide understanding of the genetics and

pathophysiology between different mutations and the chance of malignant transformation, risk stratification of patients will become further defined and decisions on which patients should proceed to curative HCT will become clearer.

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Key Points

- SCN patients who develop MDS and leukemia have an absolute indication for HCT, but have poor transplant outcomes.
- HCT with the best available donor is recommended as curative therapy for high-risk SCN, which includes patients with poor neutrophil response to high doses of G-CSF, clonal hematopoiesis in cells harboring mutations associated with MDS, or having the Gly185Arg ELANE mutation.
- Patients at low-risk for malignant transformation and infection on G-CSF therapy may be considered for HCT given the life-long risk of death from SCN complications, especially as transplant related risks decline.

Table 1

Summary of published HSCT by donor source in SCN without malignant transformation^{1,2}

Donor Source	Total Patients	Overall Survival	Event Free ³ Survival	Engraftment Failure	Acute GVHD	Chronic GVHD
Matched Related Donor (MRD)	21	20/21 (95%)	18/21 (86%)	3/21 (14%)	4/21 (19%)	3/21 (14%)
Matched Unrelated Donor (MUD)	8	7/8 (88%)	6/8 (75%)	1/8 (13%)	7/8 (88%)	0/8 (0%)
Mismatched Related Donor (MMRD)	3	1/3 (33%)	0/3 (0%)	1/3 (33%)	1/3 (33%)	1/3 (33%)
Mismatched Unrelated Donor (MMUD)	3	2/3 (67%)	2/3 (67%)	1/3 (33%)	1/3 (33%)	1/3 (33%)
Umbilical Cord	30	28/30 (93%)	13/17 (76%)	4/17 (24%)	3/12 (25%)	0/12 (0%)
Total	65	58/65 (89%)	39/52 (75%)	10/52 (19%)	16/47 (34%)	5/47 (11%)

¹ Length of follow-up post-HCT ranges from 4 months – 22.9 years

² Data is not published for every outcome resulting in an unequal number of patients for each category

³ Event free survival defined as patients alive with donor engraftment

Table 2

Summary of published HSCT by conditioning regimen in SCN without malignant transformation^{1,2}

Conditioning Type	Total Patients	Overall Survival	Event Free ³ Survival	Engraftment Failure	Acute GVHD	Chronic GVHD
Myeloablative (MA)	37	34/37 (92%)	26/33 (79%)	5/33 (15%)	9/33 (27%)	5/33 (15%)
Reduced Intensity Conditioning (RIC)	15	13/15 (87%)	9/14 (64%)	4/14 (29%)	7/14 (50%)	0/14 (0%)

¹ Length of follow-up post-HCT ranges from 4 months – 22.9 years

² Data is not published for every outcome resulting in an unequal number of patients for each category

³ Event free survival defined as patients alive with donor engraftment

Table 3

Summary of published HSCT in SCN with malignant transformation^{1,2}

Disease at transplant	Total Patients	Overall Survival	Event Free Survival	Engraftment Failure	Relapse of Disease	Acute GVHD	Chronic GVHD
MDS	7	4/7 (57%)	4/7 (57%)	0/7 (0%)	0/7 (0%)	5/6 (83%)	3/7 (43%)
Leukemia	11	4/11 (36%)	3/11 (27%)	3/11 (27%)	2/11 (18%)	6/9 (67%)	5/11 (45%)

¹ Length of follow-up post-HCT ranges from 14 months – 10.8 years

² Data is not published for every outcome resulting in an unequal number for these categories: relapse, acute GVHD, chronic GVHD