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Editorial

# Indications for hematopoietic cell transplantation for children with severe congenital neutropenia

Severe congenital neutropenia (SCN) is a hematologic condition characterized by arrested maturation of myelopoiesis at the promyelocyte stage of development (1). With appropriate treatment using recombinant human granulocyte colony-stimulating factor (r-HuG-CSF), patients with SCN are now surviving well past infancy. With longer survival, the high risk of developing myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) has become remarkedly clear (2). Hematopoietic cell transplant (HCT) is the only curative option for these patients, but the outcome is poor once MDS/AML has developed. In this issue of the journal, Oshima et al. (3) report an analysis of 18 patients with SCN in Japan who underwent HCT (1989–2005) because of the lack of or a partial response to treatment with r-HuG-CSF prior to malignant transformation to MDS/AML.

## Patients with high-risk SCN

All patients with SCN are at risk of developing MDS/AML at a rate of approximately 2.3% per year after 10 yr on r-HuG-CSF. This was recently reported in the *British Journal of Hematology* by Rosenberg et al. (4), which is substantially below the range of 4–12% per year suggested by previous Severe Congenital Neutropenia International Registry (SCNIR) data. Nonetheless, the cumulative incidence for sepsis death and malignant transformation in high-risk patients (median absolute neutrophil count [ANC] remains consistently $< 2.19 \times 10^9$/L despite being on r-HuG-CSF $> 8$ $\mu$g/kg/day) after 15 yr is 18% and 34%, respectively. These median values (8 $\mu$g/kg/day and $2.19 \times 10^9$/L) are based upon previously described interactions between the dose of r-HuG-CSF at six months and the ANC value on treatment and reflect somewhat higher target values than recommended today (5). Once the high-risk patients are identified, we believe that transplant with the best available donor is the treatment of choice. Initially, the majority of patients who underwent HCT received bone marrow from HLA-matched siblings, but the number of patients undergoing transplantation from alternative donors (haploidentical, unrelated adult donors, and unrelated cord blood transplants) is growing (6). Once patients with SCN go on to develop MDS/AML, the prognosis is dismal with mortality rates approaching 100%. Although remissions can be achieved with chemotherapy, serious infectious complications are common, and adequate neutrophil recovery can only be reliably achieved with reinstitution of r-HuG-CSF. Survival in patients who transform to malignancy therefore is dependent on undergoing a successful allogeneic HCT. We previously reported on six patients who underwent transplant for leukemic transformation and their outcomes (7). Patients who progressed to AML before transplant were at high risk of transplant-related complications and experienced high rates of mortality. Patients with high-risk SCN who undergo allogeneic HCT prior to leukemic transformation have had the best outcomes. Thus, it is imperative to identify these high-risk patients early and refer them for consideration of allogeneic HCT. At our own institution, five of the six patients who underwent transplant for lack of response to r-HuG-CSF remain alive with a median of 7.15 yr.

## Patients with low-risk SCN

In patients who receive r-HuG-CSF lower than 8 $\mu$g/kg/day and achieve a median ANC above $2.19 \times 10^9$/L (low-risk group), referral for bone marrow transplant consult should still be made

early in the treatment course because the cumulative incidence of malignant transformation still attains high levels. If a matched related donor is identified, proceeding with transplant should be considered, especially with the improved supportive care and transplant-related outcomes. This approach is similar to that taken for patients with $\beta$-thalassemia, for whom related donor transplant is the standard of care before serious complications have an opportunity to develop. For patients with SCN without an available related donor, close monitoring with routine complete blood counts and annual bone marrow examinations, including cytogenetic studies is essential. At this time, data are lacking to recommend up-front alternative donor transplantation for patients with low-risk SCN.

The relative hazard curve for malignant transformation for those patients who are able to maintain a median ANC between 1.0 and $1.5 \times 10^9$/L with daily r-HuG-CSF dosing $< 8$ $\mu$g/kg/day is not known. We suspect that it probably falls somewhere between the low- and high-risk groups. The initial analysis from the SCNIR targeted a median ANC above or below $2.19 \times 10^9$/L to confer risk stratification, low versus high groups, respectively (5). However, when the initial cohort was treated with r-HuG-CSF, the target ANC was higher than current standard practice, hence a relatively high median ANC. Therefore, similar to the approach for the low-risk group, we recommend early referral to a blood and marrow transplant team for these patients and if a matched related donor is identified, transplant should be considered.

### Conditioning regimen and graft-versus-host disease (GVHD) prophylaxis

Optimal pretransplant conditioning and GVHD prophylaxis have not been established for patients with SCN. In the Oshima analysis, there was considerable heterogeneity in approaches (3). Twelve patients received a myeloablative conditioning regimen, and six patients received a non-myeloablative conditioning regimen. There were no statistically significant differences in survival rates between the two groups. However, based on this limited number of patients, there is insufficient experience to suggest that non-myeloablative transplants should be the preferred conditioning regimen. As the authors pointed out, in the absence of leukemic transformation, patients with SCN typically do not receive chemotherapy prior to undergoing allogeneic HCT and thus have an intact T-cell repertoire. Thus, an immunoablative regimen appears to be the important factor to take into consideration in choosing the appropriate conditioning, i.e., some sort of anti-T-cell therapy, such as anti-thymocyte globulin (ATG), because of the increased risk for rejection. The high rate of graft rejection observed by Oshima et al. (3) emphasizes this point. None of the patients who rejected their grafts received ATG in their conditioning regimen. With the increasing number of agents with immunosuppressive and myelosuppressive activity, the options for conditioning regimens have broadened. Thus, it is not possible to recommend a single conditioning regimen for all patients with SCN who undergo allogeneic HCT. Patient age, comorbidities, degree of human leukocyte antigen matching, and donor source are important factors to take into consideration when selecting a conditioning regimen. Additional factors that contribute to successful engraftment following allogeneic HCT include cell dose, prior treatment, and post-transplant GVHD prophylaxis. We agree with the authors that GVHD prophylaxis should be optimized in patients with SCN undergoing transplant because they do not benefit from any graft-versus-leukemia effects if they have not transformed to MDS/AML. At present, we recommend that institutional practice guides the choice of conditioning regimen and GVHD prophylaxis.

### Summary

Allogeneic HCT is reserved for patients with SCN to high-risk patients and/or once MDS or AML develops. In these patients, allogeneic transplant with the best matched donor has evolved into a standard of care. Over time, with our improved understanding of the disease, the timing of transplantation for patients with high-risk SCN has moved earlier in the course of illness, and outcomes are better for patients transplanted prior to malignant transformation. For low-risk patients, if a related donor is available, consideration to proceed with allogeneic HCT should be made with a careful balancing of short- and long-term risk of HCT against the cumulative risk of death from malignant transformation. If a related donor is not available, balancing the known lifetime risk of leukemic transformation against the morbidity and mortality risk of allogeneic transplantation remains a challenge. At present, for most patients with r-HuG-CSF-responsive SCN, continued treatment with r-HuG-CSF will be favored over alternative donor allogeneic HCT. However, as the risk of treatment-related mortality continues

to be successfully reduced with improved strategies and supportive care measures, we expect to see more alternative donor transplants for patients with SCN.

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