

Guidelines for pediatric management of severe chronic neutropenia

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For many years, there was no effective treatment for severe chronic neutropenia. Patients were simply prescribed antibiotics, when they developed fever and infections. Recombinant human granulocyte colony-stimulating factor (G-CSF) dramatically changed this situation, when it became available for clinical studies in 1986. Soon thereafter evidence from small trials suggested that G-CSF was useful for treatment of cyclic, congenital, and idiopathic neutropenia. A randomized controlled trial then established that daily subcutaneous G-CSF, given in doses to achieve a blood neutrophil count of approximately $2.0 \times 10^9/L$, could reduce the occurrence of fever, mouth ulcers, infections, and antibiotic use in these patients [1]. Although this trial proved the efficacy of G-CSF therapy as a preventive therapy for severe chronic neutropenia, it did not provide precise guidelines for the best ways to care for these patients.

In this issue of the Journal, Fioredda et al. [2] report consensus guidelines for therapy and follow-up of children with congenital and acquired neutropenia. The report is based on a careful review of the literature and grading the evidence in 59 reports by an expert panel of Italian hematologists. The evidence in these reports was scored by the experts on a scale of 1–9. Statements receiving a mean score that was greater than 7 were regarded as appropriate/necessary clinical practices. Statements about treatment are referenced, and the level of evidence and the level and strength of the consensus are also provided. The panel is to be commended for the careful way they conducted and presented these guidelines.

Since 1994, another group, the Advisory Board for the Severe Chronic Neutropenia International Registry (SCNIR or Registry), has also engaged in developing treatment recommendations and guidelines for these patients [3–7]. The Registry's efforts are based on data from patients enrolled in the original Phase 2 and Phase 3 trials and prospectively collected data from a much larger group of patients enrolled subsequently in the Registry. The board meets annually and communicates regularly about individual patients. Annually, the board reviews new and cumulative clinical observations, by diagnostic category, by specific/genetic diagnosis, and by geographic origin. It also discusses adverse events, reviews, and revises treatment recommendations, and periodically published reports from this longitudinal, observational study.

The Italian report includes the reports and observations of the SCNIR and largely confirms its recommendations. This is important, because the SCNIR was originally sponsored by Amgen, a US manufacturer of G-CSF, and the physicians directing the SCNIR have a potential conflict of interest in making recommendations regarding this agent. By contrast, the expert panel for this report does not have this conflict, but it reached the same conclusions regarding G-CSF therapy based on its review of evidence.

This report provides recommendations about several controversial issues that differ somewhat from the recommendations and statements for the SCNIR. For example, for patients with glycogen storage disease, the report does not mention the problem of severe splenomegaly, when

these patients receive G-CSF therapy; the SCNIR advises physicians of this concern and advises using the lowest possible G-CSF dose to minimize this problem. The report advises that Shwachman–Diamond syndrome may be at greater risk of leukemic transformation and therefore advises “on-demand” G-CSF. The recommendation is not referenced, and the relationship of G-CSF treatment and the risk of leukemic transformation are not known. The SCNIR recommends continuous G-CSF for patients with severe neutropenia and recurrent fever and infections, regardless of the type of neutropenia. The report is also limited to children, but approximately half of the patients now in the SCNIR are now of adult age. The SCNIR makes recommendations for the continuum of ages, including both children and adults. Table 2 provides expert recommendations about the frequency of biochemical parameters and abdominal ultrasound; the SCNIR has not evaluated or made recommendations about these tests. Overall, however, these are minor points, and these guidelines are very useful for improving the care of patients with these rare hematological diseases.

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