Chronic idiopathic neutropenia (CIN): what we know & don’t know

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• How to diagnosis & theories about its cause
• Natural history (what to expect)
• Treatment: GCSF & safety considerations

Blood cell development

Neutrophil Maturation

These are seen in the blood


What causes an isolated low neutrophil count?

- Absolute neutrophil count < 2 standard deviations below the population average (generally <1500/μL)
- Hereditary neutropenia
  - Cyclic
  - Severe congenital
- Acquired neutropenia
  - Neonatal alloimmune (babies)
  - Primary autoimmune (kids)
  - Drug induced
  - Secondary autoimmune & LGL leukemia
  - Chronic idiopathic (CIN)

CIN: a diagnosis of exclusion

• Patient history and physical exam
  - Old blood counts (acquired neutropenia?)
  - Consider underlying illness (autoimmune disorder, cancer, infection)
  - Drug history
• Laboratory data
  - Blood counts (are other cell counts abnormal)?
    - anemia, low platelets, & increased monocyte count*
  - Antineutrophil antibody testing (controversial)
  - Consider imaging scans (looking for underlying cause)
  - Consider bone marrow biopsy

CIN: a diagnosis of exclusion

As there are no specific diagnostic findings in CIN, this diagnosis may reflect a mixture of diseases.

Chronic "nonimmune" idiopathic neutropenia: strict diagnostic criteria

- ANC < 1500/uL for African Americans and <1800/uL for Caucasians
- Absence of clinical, laboratory, or imaging studies suggesting any underlying disease that could cause neutropenia
- No drug exposures or radiation exposure
- Normal bone marrow chromosomes
- Negative antineutrophil antibodies

Antineutrophil antibody testing

Bone marrow aspirate & biopsy


Bone marrow aspirate & biopsy

The cause of CIN is poorly understood: likely has an autoimmune component

- Decreased production of neutrophils in the bone marrow
- Destruction of neutrophils (or precursors) in bone marrow or blood
- Movement of neutrophils from the blood into tissues or organs

Neutropenia lessons from T-cell large granular lymphocytic leukemia

- Leukemia of mature T cells, indolent disease
- Usually presents ~60 yo with neutropenia ± anemia ± enlarged spleen
- 1/3 of patients are asymptomatic at presentation

Diagnosis requires that you find an expanded population of clonal large granular T lymphocytes.

![Image of normal lymphocyte and LGL lymphocyte](Images modified from the American Society of Hematology Image Bank 2003.)

The cause of CIN (cont).

- Studies in some CIN patients identify increased number of activated T lymphocytes with increased inflammatory mediators that suppress neutrophils in the bone marrow.¹-³
- The cause of neutropenia in some CIN cases may be similar to the cause of neutropenia in large granular lymphocytic leukemia.

![Diagram showing the process of virus-infected cell dying and CTL cells accumulating](Virus-infected cell dies -> Accumulation of cytotoxic T lymphocytes.)

Natural history (what to expect)

- Original report of 15 patients with CIN
  - 14/15 were female, no large spleens
  - Initial ANC < 1000/uL in all patients
    - ×250/uL in 9/15 patients
  - Marrow showed absence of mature neutrophils
- Median follow-up 15 years (8-31 years)
  - 9/15 patients had persistent ANC<1000
  - No reported increase risk of infection
    - This was with NO THERAPY
    - Another study of 41 patients with CIN f/up 6 years showed a higher rate of minor to moderate infections in patients with ANC<500/uL vs. 500-1000 (56% vs. 8%).³

![Diagram showing the increase in G-CSF dose](Images of idiopathic neutropenia patients on SCNIR 1994-1999*)

Idiopathic Neutropenia Patients on the Severe Chronic Neutropenia International Registry 1994-1999*

- 238 cases of idiopathic neutropenia
  - Adult and child-onset neutropenia
  - ANC < 500/uL
  - No evidence of cancer, autoimmune disorder, or drug exposure
  - Likely includes CIN & autoimmune neutropenia
  - 69.3% female
  - G-CSF increased mean ANC from ~390/uL to 3840/uL.


<table>
<thead>
<tr>
<th>GCSF dose (ug/kg/day)</th>
<th>Congenital n = 169</th>
<th>Cyclic n = 79</th>
<th>Idiopathic n = 117</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>10.19</td>
<td>2.72</td>
<td>1.85</td>
</tr>
<tr>
<td>SD</td>
<td>19.03</td>
<td>2.28</td>
<td>2.42</td>
</tr>
<tr>
<td>Median</td>
<td>5.00</td>
<td>2.03</td>
<td>1.08</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.25</td>
<td>0.17</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum</td>
<td>190</td>
<td>10.14</td>
<td>16.67</td>
</tr>
</tbody>
</table>

Idiopathic neutropenia patients on the SCNIR 1994-1999

- No cases of leukemia or Myelodysplastic Syndrome
- Did not report details on infectious complications

Development of acute leukemia is very rare in CIN (6 reported cases). CIN patients are not thought to be at higher risk of leukemia.

Therapy

Treat the patient & not the numbers!

GCSF should be reserved for those patients with significant recurrent infectious complications and considered in those with severe neutropenia.

Neutrophil Production & where GCSF acts

Marrow

- STEM CELL → CFU-GM → GM-CSF → G-CSF → 7 Days
- NEUTROPHIL → MYELOCYTE → MYELOBLAST → 14 Days

Peripheral Blood

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Peripheral Blood

Tissue

- CYTOKINE RELEASE → NEUTROPHIL → RESPIRATORY BURST → PHAGOCYTOSIS

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- CIRCULATING POOL (50%) → MARGINAL POOL (50%) → 6-10 Hours

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GCSF & safety:

adverse events reported in different populations

- Bone pain is the most commonly reported adverse event in peripheral blood stem cell donors (PBSC). Generally treated with acetaminophen or ibuprofen
- Splenic rupture
  - Spleen size increased in 95% of PBSC donors (mean length increase of 13%) and size returned to baseline 10 days after GCSF stopped.
  - 11 cases of splenic rupture
    - All receiving short course of GCSF

GCSF & safety:
adverse events reported in different populations

• Rare reported events¹
  - Serious skin rash (cutaneous vasculitis)
  - Lung injury
  - Thyroid dysfunction

• No studies to date proving GSCF-therapy causes leukemia or myelodysplastic syndrome
  - Thus far, no association in PBSC donors established.¹
  - In severe congenital neutropenia the dose of G-CSF is associated with the risk of leukemia and myelodysplastic syndrome, but this does not prove GCSF has a role in leukemia.²


The End