The Burden of Chemotherapy-Induced Myelosuppression in Patients with Small Cell Lung Cancer: What’s New?

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Touchpoints

- Chemotherapy-induced myelosuppression (CIM) today and beyond
- Current therapies and clinical recommendations for managing CIM
- Health economic & patient-reported experience
  - Redefining the real-world impact of CIM
- Investigational therapies focused on the root of the problem
Chemotherapy-induced myelosuppression (CIM) today... and beyond
Hematopoiesis describes the formation of new blood cells.

- Hematopoiesis occurs within the hematopoietic system, which includes bone marrow, liver, and spleen.
- The process begins with undifferentiated HSCs that transform into myeloid or lymphoid progenitor cells.
- Progenitor cells divide and mature into blood components, such as RBCs, WBCs, and platelets.

Myelosuppression

- A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets.
  - Results from impaired hematopoietic stem and progenitor cells in bone marrow (BM) and peripheral blood\(^1,2\)
  - Can be a lasting effect of cytotoxic chemotherapy that dampens the antitumor immune response\(^2\)

- Increases morbidity and mortality\(^1\)
  - Higher risk of infections, bleeding complications
  - Long-term BM toxicity can result in myelodysplastic syndrome (MDS), acute leukemias, and BM exhaustion\(^2\)

- Impacts patient safety, quality of life (QoL), and imposes costs to the healthcare system

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Cancer chemotherapy target cells at different phases of the cell cycle

- Cell-cycle–specific chemotherapy drugs act in one (or two) phases of the cycle\(^1\)
- Cell-cycle–nonspecific drugs are active across all phases\(^1\)
- Some chemotherapy drugs can inhibit cell proliferation by arresting cells in specific phases of the cell cycle\(^2\)
- Chemotherapy is effective at killing cells that are rapidly dividing\(^1\)

Figure adapted from: [http://chemoth.com/cellcycle](http://chemoth.com/cellcycle).
Chemotherapy remains the cornerstone of treatment for patients with SCLC

- Lung cancer is the leading cause of cancer-related death in the US and around the world¹
- SCLC accounts for ~13% of all lung cancer cases in the US, with most patients diagnosed at an advanced stage²,³
- Prognosis is poor, with a 5-year survival rate of 6%, decreasing to 3% among patients with distant metastasis²
- Systemic chemotherapy, alone or in combination with immune checkpoint inhibitors, is the standard of care for patients with advanced SCLC⁴

Standard-of-care chemotherapy regimens for SCLC present a treatment challenge due to clinically significant, multilineage myelosuppression⁵

Despite current treatment options, myelosuppression remains a common consequence of chemotherapy

- CIM is typically managed with dose delays and reductions, in addition to prophylactic or supportive interventions\(^1\)–\(^5\)

<table>
<thead>
<tr>
<th>Condition (fewer)</th>
<th>1L SCLC incidence of Grade 3/4(^6)</th>
<th>2L SCLC incidence of Grade 3/4(^7)</th>
<th>Current treatment</th>
<th>Unmet need/burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>23%</td>
<td>54% (3% FN)</td>
<td>G-CSF rescue</td>
<td>~70% bone pain (~25% severe)(^9) induced by G-CSFs (severe pain treated with NSAIDs, antihistamines, and opioids)</td>
</tr>
<tr>
<td>Anemia</td>
<td>14%</td>
<td>31%</td>
<td>ESA rescue, transfusion rescue</td>
<td>ESA box warning for shortened OS and increased risk of tumor progression; increased risk of myocardial infarction, stroke, thrombosis of vascular access, venous thromboembolism, and death(^10)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10%</td>
<td>54%</td>
<td>Transfusion rescue</td>
<td>No options other than transfusions(^4)</td>
</tr>
</tbody>
</table>

Myelosuppression is currently an unavoidable consequence of chemotherapy that impacts patient safety, quality of life, and costs to the health care system

Chemotherapy-Induced Neutropenia (CIN)

- Common yet serious adverse event (AE) following myelosuppressive chemotherapy
- Risk factors can be
  - Patient specific
  - Disease specific
  - Treatment specific
- Absolute neutrophil count (ANC) <1,000/µL; clinically significant when ANC is <500/µL
  - Febrile neutropenia (FN) occurs when ANC < 500/µL or is anticipated to decline within 48 hours accompanied by a fever of ≥38.3°C
- Most common reason for dose delays/reductions, which can compromise patient outcomes

What is neutropenia?

Neutropenia is a low number of neutrophils in the blood

- Normal blood cells under the microscope
- Neutrophil
- RBC
- Platelet
- ANC greater than 1500 per microliter of blood
- ANC less than 1500 per microliter of blood

Figure adapted from: https://jamanetwork.com/journals/jamaoncology/fullarticle/2645851.

Consequences of CIN

- The risk of FN increases with the duration of severe neutropenia\(^1\)
- FN is associated with\(^2\):
  - Prolonged hospitalizations
  - Serious infections
  - Use of broad-spectrum antibiotics
  - Decreased QoL
  - Increased mortality

Abbreviations: ANC, absolute neutrophil count; FN, febrile neutropenia.


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Chemotherapy-Induced Anemia (CIA)

- CIA occurs in 30%–90% of patients\(^1\)
  - Incidence is highly variable\(^2\)
- In addition to tumor type and regimen, risk factors for CIA include older age, comorbidities, and poor performance status\(^2\)
- Hemoglobin level ≤11 g/dL should prompt an evaluation in cancer patients\(^1\)
  - In patients with high baseline Hgb level, a drop of ≥2 g/dL may be cause for concern

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Figure adapted from: https://www.aboutkidshealth.ca/Article?contentid=841&language=English.
Hemoglobin Level is Associated with QoL

- CIA can cause:
  - fatigue
  - pale skin
  - dyspnea
  - drowsiness
  - depression
  - tachycardia
  - dizziness

- Consequences of CIA can lead to chemotherapy delays and a negative effect on QoL.

- CIA is associated with increased morbidity, mortality, and healthcare costs.


Abbreviations: Hgb, hemoglobin; LASA, Linear Analog Scale Assessment; QOL, quality of life.
Chemotherapy-Induced Thrombocytopenia (CIT)

- Although CIT commonly occurs, limited data is available on its incidence in the US\textsuperscript{1}
- Most standard regimens have relatively low rates of CIT, with durations of 4 to 6 days\textsuperscript{2}
  - Highest rates are associated with anthracycline-, gemcitabine-, and platinum-based regimens\textsuperscript{3}
- CIT is defined as platelet count $<100,000/\mu$L, with or without bleeding\textsuperscript{4}
- Major consequences include dose delays/reductions and a decrease in relative dose intensity, which can adversely affect treatment outcomes and increase healthcare costs\textsuperscript{1,2,5}

\begin{itemize}
\end{itemize}
Consequences of Myelosuppressive Chemotherapy

Abbreviations: FN, febrile neutropenia.

MYELOSUPPRESSIVE CHEMOTHERAPY

Neutropenia

Thrombocytopenia

Bleeding or excessive bruising

Chemotherapy dose delays and dose reductions

Decreased relative dose intensity (RDI)

Increased morbidity, mortality, and healthcare costs

Anemia

Fatigue, dizziness, tachycardia, dyspnea

Complicated life-threatening infection and prolonged hospitalization

FN
Current therapies and clinical recommendations for managing CIM
Hematopoietic Rescue Therapies for Chemotherapy-Induced Myelosuppression

- Chemotherapy damages the stem cell in the BM resulting in
  - Damage to all downstream cell lines, including committed progenitor cells
  - Impairment of HSC self-renewal
  - Decreased HSC reserve

- G-CSFs and ESAs are
  - Rescue therapies after damage to BM by chemotherapy has already occurred
  - Lineage-specific and thus only promote proliferation of neutrophils and erythrocytes

Abbreviations: BM, bone marrow; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte-colony-stimulating factor; HSC, hematopoietic stem cell; HSPC, hematopoietic stem progenitor cell.
Abbreviations: OBI, on-body injector; WBC, white blood cell.

*Tbo-filgrastim approval in 2012 was before implementation of the FDA’s biosimilar approval process.

NCCN Recommendations for G-CSF

**Primary Prophylaxis**

- **High FN Risk (≥20%)**
  - Administer filgrastim 5 μg/kg SQ beginning the day (or up to 3-4 days) after chemotherapy and continue until post nadir ANC recovery
  - OR
  - Administer pegfilgrastim 6 mg SQ* × 1 dose the day after chemotherapy. There should be at least 12 days between the dose of pegfilgrastim and the next chemotherapy cycle.

- **Intermediate FN Risk (10% to 20%)**
  - Consider G-CSF based on patient-specific risk factors, including prior chemotherapy or radiotherapy, persistent neutropenia, BM involvement, recent surgery, liver or renal dysfunction, and age ≥55 years

- **Low FN Risk (<10%)**
  - No G-CSF

**Secondary Prophylaxis**

- FN in prior cycle
  - YES
  - If prior G-CSF, then consider dose reduction or treatment change
  - NO
  - If no prior G-CSF, then consider G-CSF as dosed above

**Treatment**

- Presents with FN
  - If currently receiving a daily G-CSF, then continue treatment
  - If received a long-acting G-CSF, then no further G-CSF
  - If no prior G-CSF and no risk factors for FN, then therapeutic G-CSF is not recommended
  - If no prior G-CSF and risk factors for an infection-related complication present, then G-CSF

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NCCN, National Comprehensive Cancer Network; SQ, subcutaneous.

*Alternatively, the pegfilgrastim on-body injector can be used.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.2.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org.
Abbreviations: FDA, Food and Drug Administration; NCCN, National Comprehensive Cancer Network.

# NCCN Recommendations for ESAs

**CONSIDER ESAs FOR**

- Patients undergoing palliative treatment
- Select patients who refuse RBC transfusions
- Patients with cancer and chronic kidney disease
- Patients on myelosuppressive chemotherapy without any other identifiable cause for anemia

## ESA

<table>
<thead>
<tr>
<th>ESA</th>
<th>Side Effects and Considerations for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin alfa (Epogen® or Procrit®, Amgen)</td>
<td>- Increased mortality in some populations</td>
</tr>
<tr>
<td>Biosimilar epoetin alfa: Epoetin alfa-epbx (Retacrit®, Pfizer)</td>
<td>- May stimulate tumor growth</td>
</tr>
<tr>
<td>Darbepoetin alfa (Aranesp®, Amgen)</td>
<td>- Should not be used when the anticipated outcome is cure</td>
</tr>
<tr>
<td></td>
<td>- Not all diseases respond to ESAs</td>
</tr>
<tr>
<td></td>
<td>- Payors may be hesitant to cover ESAs due to the risks associated with use</td>
</tr>
</tbody>
</table>

Abbreviations: ESA, erythropoiesis-stimulating agent; NCCN, National Comprehensive Cancer Network.
ASCO Recommendations for Platelet Transfusions

Prophylactic versus Therapeutic Platelet Transfusions

- Prophylactic transfusions should be administered to patients with impaired BM function to reduce the risk of hemorrhage

Thresholds for Prophylactic Platelet Transfusions

- Recommended threshold for solid tumors and hematologic malignancies is <10 × 10^9/L
  - Solid tumors:
    • Risk of bleeding is related to the depth and duration of the platelet nadir
    • Higher threshold is appropriate for active localized bleeding
  - Hematologic malignancies:
    • Higher threshold may be advisable in certain circumstances
<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy-Induced Neutropenia</strong></td>
</tr>
<tr>
<td>Expand primary prophylactic use of G-CSF to minimize risk of FN</td>
</tr>
<tr>
<td>• Revised threshold for use of G-CSF from use with only high-risk regimens (&gt;20%) to intermediate-risk (10%–20%) or high-risk regimens</td>
</tr>
<tr>
<td>• Expanded therapeutic use for patients not previously on G-CSF who develop FN to all patients, not just those with a risk factor for complication</td>
</tr>
<tr>
<td>• Consider using G-CSF to accelerate post-HCT recovery to minimize days of hospitalization</td>
</tr>
<tr>
<td>• Consider self administration or use of on-body injector to minimize visits to outpatient center</td>
</tr>
<tr>
<td>• Avoid G-CSF in case of respiratory infection, respiratory symptoms, or confirmed or suspected COVID-19</td>
</tr>
</tbody>
</table>

| **Chemotherapy-Induced Anemia** |
| • Consider restricting threshold for RBC transfusion (eg, Hgb < 7 g/dL) |
| • Broaden use of ESAs ± IV iron to manage anemia given the blood supply shortages |

| **Chemotherapy-Induced Thrombocytopenia** |
| • Lowered threshold for platelet transfusion to $10 \times 10^9$/L, modified for patients with bleeding |
| • Consider thrombopoietin mimetics (eg, romiplostim) for patients with severe thrombocytopenia post chemotherapy (platelet level threshold of 30–50 $\times 10^9$/L to start) |

Abbreviations: ESA, erythropoiesis-stimulating agent; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; Hgb, hemoglobin; HCT, hematopoietic cell transplantation; NCCN, National Comprehensive Cancer Network; RBC, red blood cell; IV, intravenous.
Summary of the Current Landscape of Chemotherapy-Induced Myelosuppression Treatment

- Current strategies for the management of chemotherapy-induced myelosuppression are largely reactive
- Proactive use of currently available products is limited
  - G-CSFs can be used proactively, but only in a restricted subset of patients
  - ESAs are not used proactively due to black box warnings and risk of adverse events
- Current drug therapy strategies stimulate production of a single cell lineage (i.e., granulocyte, erythrocyte, thrombocyte)
  - No approved therapies for CIT are currently available
- Alternative strategies are needed

Abbreviations: ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor.
Health economic & patient-reported experience
— Redefining the real-world impact of CIM
Real-World Management of Chemotherapy-Induced Myelosuppression

- Online survey of 301 participants who had received chemotherapy in the last 12 months and experienced at least one episode of myelosuppression
  - Most patients (88%) considered myelosuppression to have a moderate or major impact on quality of life
    - Impact was significantly higher in patients <50 years compared with those ≥50 years of age

Patient Report of Myelosuppression Diagnosis

- Neutropenia
- Anemia
- Thrombocytopenia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Breast Cancer</th>
<th>Lung Cancer</th>
<th>Colorectal Cancer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>31%</td>
<td>36%</td>
<td>38%</td>
<td>34%</td>
</tr>
<tr>
<td>Anemia</td>
<td>67%</td>
<td>51%</td>
<td>63%</td>
<td>61%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>52%</td>
<td>61%</td>
<td>77%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Table showing the percentage of patients reporting each type of myelosuppression across different cancer types and the total.

Despite available rescue interventions, chemotherapy dose delays, reductions, discontinuations, or regimen changes were reported by 2/3 of patients.
Real-World Management of Chemotherapy-Induced Myelosuppression

Patient-Reported Side Effect Management

Oncologist warned me to expect side effects from my chemotherapy

Oncologist treated my side effects quickly

Oncologist did not treat my side effects from myelosuppression

Oncologist did not understand the level of discomfort from my side effects

Abbreviations: CRC, colorectal cancer; SE, side effect.
Real-World Financial Burden of Chemotherapy-Induced Myelosuppression in SCLC

<table>
<thead>
<tr>
<th>Event</th>
<th>Percentage</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 CIN</td>
<td>45</td>
<td>Chemotherapy-induced neutropenia</td>
</tr>
<tr>
<td>Grade 3/4 CIA</td>
<td>41</td>
<td>Chemotherapy-induced anemia</td>
</tr>
<tr>
<td>Grade 3/4 CIT</td>
<td>25</td>
<td>Chemotherapy-induced thrombocytopenia</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>43</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Prophylactic G-CSF</td>
<td>6</td>
<td>Granulocyte colony-stimulating factor</td>
</tr>
<tr>
<td>Treatment with G-CSF</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>ESA treatment</td>
<td>4</td>
<td>Erythropoiesis-stimulating agent</td>
</tr>
</tbody>
</table>

**Average Annual Per Patient Costs for Grade 3/4 Hematologic Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>$131,047</td>
</tr>
<tr>
<td>Anemia</td>
<td>$95,954</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>$90,053</td>
</tr>
</tbody>
</table>

Note: Average total cost of care for patients without grade 3/4 myelosuppression was $67,802.

Abbreviations: CIA, chemotherapy-induced anemia; CIN, chemotherapy-induced neutropenia; CIT, chemotherapy-induced thrombocytopenia; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; RBC, red blood cell; SCLC, small cell lung cancer.

Investigational therapies focused on the root of the problem
## Investigational Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Affect on HSC Lineage</th>
<th>Phase of Study</th>
<th>Active Trials as of July 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benegrastim (F627)</td>
<td>WBC-GF</td>
<td>Stimulates neutrophils</td>
<td>Phase 3</td>
<td>Trials completed in breast cancer</td>
</tr>
<tr>
<td>Eflapegrastim</td>
<td>WBC-GF</td>
<td>Stimulates neutrophils</td>
<td>Phase 1</td>
<td>TC followed by eflapegrastim as 1L in ESBC</td>
</tr>
</tbody>
</table>
| Plinabulin      | Oral vascular microtubule disrupting agent | Accelerates neutrophil maturation and delays apoptosis | Phase 1/2/3   | Plinabulin + nivolumab in NSCLC  
Nivolumab + ipilimumab + plinabulin in recurrent SCLC  
Plinabulin vs pegfilgrastim in BC patients on TAC  
Plinabulin vs pegfilgrastim after docetaxel in solid tumors  
Docetaxel ± plinabulin in advanced NSCLC |
| Roxadustat      | Oral HIF-PH inhibitor | Stimulates erythrocytes                | Phase 2/3      | Non-myeloid malignancies in patients receiving chemotherapy  
Low-risk MDS                                                                                       |
| Trilaciclib     | Intravenous CDK4/6 inhibitor | Protects neutrophils, erythrocytes, and platelets | Phase 1/2/2    | EP ± trilaciclib as 1L in SCLCa  
EP + atezolizumab ± trilaciclib as 1L in SCLC  
Topotecan ± trilaciclib as 2L/3L in SCLC  
Carboplatin + gemcitabine ± trilaciclib in TNBC                                                  |

**Abbreviations:** 1L, 2L, 3L, first-, second-, third-line; BC, breast cancer; CDK, cyclin-dependent kinase; EP, etoposide-carboplatin; ESBC, early-stage breast cancer; HIF-PH, hypoxia-inducible factor prolyl hydroxylase; MDS, myelodysplastic syndrome; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TAC, docetaxel-doxorubicin-cyclophosphamide; TC, docetaxel-cyclophosphamide; TNBC, triple-negative breast cancer; WBC-GF, white blood cell growth factor.

*Trial completed.

Despite the availability of hematopoietic rescue therapies, chemotherapy-induced myelosuppression remains an unmet clinical need

- Dose delays and dose reductions remain a significant problem, which can impact outcomes
- Some supportive care therapies are associated with adverse events, and, in certain cases, an increased risk for mortality
- Existing therapies are lineage-specific, largely reactive, and expensive
  - No approved treatments for CIT are currently available
- No therapy mitigates or protects from the myelosuppressive effects of chemotherapy before they occur
  - Discovering ways to protect HSPCs from the cytotoxic effects of chemotherapy could circumvent the development and consequences of myelosuppression
Thank you for your attention

Tell us what you think